

## COMPOUNDS AND METHODS

### FIELD OF THE INVENTION

Compounds of this invention are non-peptide, reversible inhibitors of  
5 type 2 methionine aminopeptidase, useful in treating conditions mediated by  
angiogenesis, such as cancer, haemangioma, proliferative retinopathy,  
rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular  
neovascularization and obesity.

### 10 BACKGROUND OF THE INVENTION

In 1974, Folkman proposed that for tumors to grow beyond a critical  
size and to spread to form metastases, they must recruit endothelial cells from  
the surrounding stroma to form their own endogenous microcirculation in a  
process termed angiogenesis (Folkman J. (1974) *Adv Cancer Res.* 19; 331).  
15 The new blood vessels induced by tumor cells as their life-line of oxygen and  
nutrients also provide exits for cancer cells to spread to other parts of the  
body. Inhibition of this process has been shown to effectively stop the  
proliferation and metastasis of solid tumors. A drug that specifically inhibits  
this process is known as an angiogenesis inhibitor.

20 Having emerged as a promising new strategy for the treatment of  
cancer, the anti-angiogenesis therapy ("indirect attack") has several advantages  
over the "direct attack" strategies. All the "direct attack" approaches such as  
using DNA damaging drugs, antimetabolites, attacking the RAS pathway,  
restoring p53, activating death programs, using aggressive T-cells, injecting  
25 monoclonal antibodies and inhibiting telomerase, etc., inevitably result in the  
selection of resistant tumor cells. Targeting the endothelial compartment of  
tumors as in the "indirect attack", however, should avoid the resistance  
problem because endothelial cells do not exhibit the same degree of genomic  
instability as tumor cells. Moreover, anti-angiogenic therapy generally has  
30 low toxicity due to the fact that normal endothelial cells are relatively  
quiescent in the body and exhibit an extremely long turnover. Finally since  
the "indirect attack" and "direct attack" target different cell types, there is a  
great potential for a more effective combination therapy.

More than 300 angiogenesis inhibitors have been discovered, of which  
35 about 31 agents are currently being tested in human trials in treatment of  
cancers (Thompson, et al., (1999) *J Pathol* 187, 503). TNP-470, a  
semisynthetic derivative of fumagillin of *Aspergillus fuigatus*, is among the

most potent inhibitors of angiogenesis. It acts by directly inhibiting endothelial cell growth and migration *in vitro and in vivo* (Ingber et al. (1990) *Nature* 348, 555). Fumagillin and TNP-470, have been shown to inhibit type 2 methionine aminopeptidase (hereinafter MetAP2) by irreversibly modifying its active site. The biochemical activity of fumagillin analogs has been shown to correlate to their inhibitory effect on the proliferation of human umbilical vein endothelial cells (HUVEC). Although the mechanism of the selective action of fumagillin and related compounds on MetAP2-mediated endothelial cell cytostatic effect has not yet been established, possible roles of MetAP2 in cell proliferation have been suggested.

First, hMetAP-2-catalyzed cleavage of the initiator methionine of proteins could be essential for releasing many proteins that, after myristoylation, function as important signaling cellular factors involved in cell proliferation. Proteins known to be myristoylated include the src family tyrosine kinases, the small GTPase ARF, the HIV protein nef and the  $\alpha$  subunit of heterotrimeric G proteins. A recently published study has shown that the myristoylation of nitric oxide synthase, a membrane protein involved in cell apoptosis, was blocked by fumagillin (Yoshida, et al. (1998) *Cancer Res.* 58(16), 3751). This is proposed to be an indirect outcome of inhibition of MetAP2-catalyzed release of the glycine-terminal myristoylation substrate. Alternatively, MetAP enzymes are known to be important to the stability of proteins *in vivo* according to the "N-end rule" which suggests increased stability of methionine-cleaved proteins relative to their N-terminal methionine precursors (Varshavsky, A (1996) *Proc. Natl. Acad. Sci. U.S.A.* 93, 12142). Inhibition of hMetAP2 could result in abnormal presence or absence of some cellular proteins critical to the cell cycle.

Methionine aminopeptidases (MetAP) are ubiquitously distributed in all living organisms. They catalyze the removal of the initiator methionine from newly translated polypeptides using divalent metal ions as cofactors. Two distantly related MetAP enzymes, type 1 and type 2, are found in eukaryotes, which at least in yeast, are both required for normal growth; whereas only one single MetAP is found in eubacteria (type 1) and archaeobacteria (type 2). The N-terminal extension region distinguishes the methionine aminopeptidases in eukaryotes from those in procaryotes. A 64-amino acid sequence insertion (from residues 381 to 444 in hMetAP2) in the catalytic C-terminal domain distinguishes the MetAP-2 family from the MetAP-1 family. Despite the difference in the gene structure, all MetAP

enzymes appear to share a highly conserved catalytic scaffold termed "pita-bread" fold (Bazan, et al. (1994) *Proc. Natl. Acad. Sci. U.S.A.* 91, 2473), which contains six strictly conserved residues implicated in the coordination of the metal cofactors.

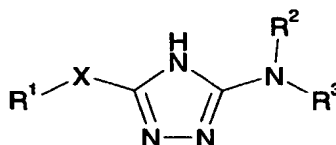
5 Mammalian type 2 methionine aminopeptidase has been identified as a bifunctional protein implicated by its ability to catalyze the cleavage of N-terminal methionine from nascent polypeptides (Bradshaw, et al (1998) *Trends Biochem. Sci.* 23, 263) and to associate with eukaryotic initiation factor 2 $\alpha$  (eIF-2 $\alpha$ ) to prevent its phosphorylation (Ray, et al. (1992) *Proc. Natl. Acad. Sci. U.S.A.* 89, 539). Both the genes of human and rat MetAP2 were cloned and have shown 92% sequence identity (Wu, et al. (1993) *J Biol. Chem.* 268, 10796; Li, X. & Chang, Y.-H. (1996) *Biochem. & Biophys. Res. Comm.* 227, 152). The N-terminal extension in these enzymes is highly charged and consists of two basic polylysine blocks and one aspartic acid block, which has  
10 been speculated to be involved in the binding of eIF-2 $\alpha$  (Gupta, et al. (1993) in *Translational Regulation of Gene Expression 2* (Ilan, J., Ed.), pp. 405-431, Plenum Press, New York).

The anti-angiogenic compounds, fumagillin and its analogs, have been shown to specifically block the exo-aminopeptidase activity of hMetAP2  
20 without interfering with the formation of the hMetAP2 : eIF2 $\alpha$  complex (Griffith, et al., (1997) *Chem. Biol.* 4, 461; Sin, et al. (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94, 6099). Fumagillin and its analogs inactivate the enzymatic activity of hMetAP2 with a high specificity, which is underscored by the lack of effect of these compounds on the closely related type 1 methionine  
25 aminopeptidase (MetAP1) both *in vitro* and *in vivo* in yeast (Griffith, et al., (1997) *Chem. Biol.* 4, 461; Sin, et al. (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94, 6099). The extremely high potency (IC<sub>50</sub> < 1 nM) of these inhibitors appears to be due to the irreversible modification of the active site residue, His231, of hMetAP2 (Liu, et al. (1998) *Science* 282, 1324). Disturbance of MetAP2  
30 activity *in vivo* impairs the normal growth of yeast (Griffith, et al., (1997) *Chem. Biol.* 4, 461; Sin, et al. (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94, 6099; In-house data) as well as *Drosophila* (Cutforth & Gaul (1999) *Mech. Dev.* 82, 23). Most significantly, there appears to be a clear correlation between the inhibition effect of fumagillin related compounds against the enzymatic  
35 activity of hMetAP2 *in vitro* and the suppression effect of these compounds against tumor-induced angiogenesis *in vivo* (Griffith, et al., (1997) *Chem. Biol.* 4, 461).

Cancer is the second leading cause of death in the U.S., exceeded only by heart disease. Despite recent successes in therapy against some forms of neoplastic disease, other forms continue to be refractory to treatment. Thus, cancer remains a leading cause of death and morbidity in the United States and elsewhere (Bailar and Gornik (1997) *N Engl J Med* 336, 1569). Inhibition of hMetAP2 provides a promising mechanism for the development of novel anti-angiogenic agents in the treatment of cancers. It has now been discovered that compounds of formulae (I) and (IA) are effective inhibitors of hMetAP2, and thus would be useful in treating conditions mediated by hMetAP2.

## SUMMARY OF THE INVENTION

In one aspect, the present invention is to a compound of formula (I), or a pharmaceutically active salt or solvate thereof, and its use in treating conditions mediated by angiogenesis, such as cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization and obesity:



Formula (I)

wherein:

X is S or O;

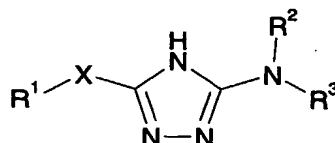
R<sup>1</sup> is optionally substituted C<sub>2-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, or C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl;

R<sup>2</sup> is optionally substituted C<sub>2-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl, provided that when R<sup>2</sup> is optionally substituted Het-C<sub>0</sub>alkyl, and Het is indole, benzofuran, benzothiophene, benzisoxazole, benzothiazole or benzopyrazole, then the optional substituent is not -(CH<sub>2</sub>)<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>; and

R<sup>3</sup> is H, optionally substituted C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, or C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl, C<sub>0-6</sub>alkyl-C(O)X'AB, C<sub>0-6</sub>alkyl-

S(O)<sub>2</sub>X'AB, C<sub>0-6</sub>alkyl-X'AB, wherein X' is O, S, C or N; A and B are independently H, optionally substituted C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl, or A or B are independently  
 5 absent, provided that the compound is not 5-anilino-3-benzylthio-1,2,4-triazole, 3-(4-methyl-anilino)-5-benzylthio-1,2,4-triazole, 3-(2-methyl-anilino)-5-benzylthio-1,2,4-triazole, 3-(4-methoxy-anilino)-5-benzylthio-1,2,4-triazole, 3-(2-methoxy-anilino)-5-benzylthio-1,2,4-triazole, or 3-ethyl-3-anilino-5-benzylthio-1,2,4-triazole.

10 In a second aspect, the present invention is to a method of treating conditions mediated by angiogenesis, such as cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization and obesity by administering a compound of formula (IA), or a pharmaceutically acceptable  
 15 salt or solvate thereof



Formula (IA)

wherein,

X is S or O;

20 R<sup>1</sup> is optionally substituted C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, or C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl;

R<sup>2</sup> is optionally substituted C<sub>2-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl;  
 25

R<sup>3</sup> is H, optionally substituted C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, or C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl, C<sub>0-6</sub>alkyl-C(O)X'AB, C<sub>0-6</sub>alkyl-S(O)<sub>2</sub>X'AB, C<sub>0-6</sub>alkyl-X'AB, wherein X' is O, S, C or N; A and B are  
 30 independently H, optionally substituted C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl, or A or B are independently absent.

In another aspect, the present invention is to a method of inhibiting  
 35 MetAP2 in the treatment of angiogenesis-mediated diseases, all in mammals,

preferably humans, comprising administering to such mammal in need thereof, a compound of formula (IA), or a pharmaceutically active salt or solvate thereof.

In yet another aspect, the present invention is to pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier therefor. In particular, the pharmaceutical compositions of the present invention are used for treating MetAP2-mediated diseases.

## DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that substituted 1,2,4-triazoles of formulae (I) and (IA) are inhibitors of MetAP2. It has also now been discovered that selective inhibition of MetAP2 enzyme mechanisms by treatment with the inhibitors of formula (IA), or a pharmaceutically acceptable salt or solvate thereof, represents a novel therapeutic and preventative approach to the treatment of a variety of disease states; including, but not limited to, cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization and obesity.

The term "C<sub>1-6</sub>alkyl" as used herein at all occurrences means a substituted and unsubstituted, straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl, pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. Any C<sub>1-6</sub>alkyl group may be optionally substituted independently by one or more of OR<sup>4</sup>, R<sup>4</sup>, NR<sup>4</sup>R<sup>5</sup>. C<sub>0</sub>alkyl means that no alkyl group is present in the moiety. Thus, Ar-C<sub>0</sub>alkyl is equivalent to Ar.

As used herein at all occurrences, substituents R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are independently defined as C<sub>2-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, Ar-C<sub>0-6</sub>alkyl, Het-C<sub>0-6</sub>alkyl, or C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl.

The term "C<sub>3-7</sub>cycloalkyl" as used herein at all occurrences means substituted or unsubstituted cyclic radicals having 3 to 7 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl radicals.

The term "C<sub>3-6</sub>alkenyl" as used herein at all occurrences means an alkyl group of 3 to 6 carbons wherein a carbon-carbon single bond is replaced by a carbon-carbon double bond. C<sub>3-6</sub>alkenyl includes 1-propene, 2-propene, 1-butene, 2-butene, isobutene and the several isomeric pentenes and hexenes. Both cis and trans isomers are included within the scope of this invention.

Any C<sub>3-6</sub>alkenyl group may be optionally substituted independently by one or more of Ph-C<sub>0-6</sub>alkyl, Het'-C<sub>0-6</sub> alkyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>mercaptyl, Ph-C<sub>0-6</sub>alkoxy, Het'-C<sub>0-6</sub>alkoxy, OH, NR<sup>4</sup>R<sup>5</sup>, Het'-S-C<sub>0-6</sub>alkyl, (CH<sub>2</sub>)<sub>1-6</sub>OH, (CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, O(CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, (CH<sub>2</sub>)<sub>0-6</sub>CO<sub>2</sub>R<sup>6</sup>,  
 5 O(CH<sub>2</sub>)<sub>1-6</sub>CO<sub>2</sub> R<sup>6</sup>, (CH<sub>2</sub>)<sub>1-6</sub>SO<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub> or halogen.

The term "C<sub>3-6</sub>alkynyl" as used herein at all occurrences means an alkyl group of 3 to 6 carbons wherein one carbon-carbon single bond is replaced by a carbon-carbon triple bond. C<sub>3-6</sub> alkynyl includes 1-propyne, 2-propyne, 1-butyne, 2-butyne, 3-butyne and the simple isomers of pentyne and  
 10 hexyne.

The terms "Ar" or "aryl" as used herein interchangeably at all occurrences mean phenyl and naphthyl, optionally substituted by one or more of Ph-C<sub>0-6</sub>alkyl, Het'-C<sub>0-6</sub> alkyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>mercaptyl, Ph-C<sub>0-6</sub>alkoxy, Het'-C<sub>0-6</sub>alkoxy, OH, NR<sup>4</sup>R<sup>5</sup>, Het'-S-C<sub>0-6</sub>alkyl, (CH<sub>2</sub>)<sub>1-6</sub>OH,  
 15 (CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, O(CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, (CH<sub>2</sub>)<sub>0-6</sub>CO<sub>2</sub>R<sup>6</sup>, O(CH<sub>2</sub>)<sub>1-6</sub>CO<sub>2</sub> R<sup>6</sup>, (CH<sub>2</sub>)<sub>1-6</sub>SO<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub> or halogen; in addition, Ph may be optionally substituted with one or more of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, OH, (CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, O(CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, CO<sub>2</sub>R<sup>6</sup>, CF<sub>3</sub>, or halogen; Het' is defined as for Het, and may be optionally substituted by one or more of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, OH, (CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, O(CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, CO<sub>2</sub>R<sup>6</sup>, CF<sub>3</sub>, or halogen;  
 20 or two C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy groups may be combined to form a 5-7 membered, saturated or unsaturated ring, fused onto the Ar ring.

Suitably, for compounds of formula (I), when Ar is substituted by Ph or Het', then Ph or Het' are substituted with one or more of C<sub>2-6</sub>alkyl, C<sub>1-6</sub>alkoxy, (CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, O(CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, CO<sub>2</sub>R<sup>6</sup>, CF<sub>3</sub> or halogen.  
 25

The terms "Het" or "heterocyclic" as used herein interchangeably at all occurrences, mean a stable 5- to 7-membered monocyclic, a stable 7- to 10-membered bicyclic, or a stable 11- to 18-membered tricyclic heterocyclic ring, all of which are either saturated or unsaturated, and consist of carbon atoms  
 30 and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any  
 35 heteroatom or carbon atom which results in the creation of a stable structure.

It will be understood that Het may be optionally substituted with one or more of Ph-C<sub>0-6</sub>alkyl, Het'-C<sub>0-6</sub> alkyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>mercaptyl, Ph-C<sub>0-6</sub>alkoxy, Het'-C<sub>0-6</sub>alkoxy, OH, NR<sup>4</sup>R<sup>5</sup>, Het'-S-C<sub>0-6</sub>alkyl, (CH<sub>2</sub>)<sub>1-6</sub>OH, (CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, O(CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, (CH<sub>2</sub>)<sub>0-6</sub>CO<sub>2</sub>R<sup>6</sup>,  
 5 O(CH<sub>2</sub>)<sub>1-6</sub>CO<sub>2</sub> R<sup>6</sup>, (CH<sub>2</sub>)<sub>1-6</sub>SO<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, CN, or halogen; Ph may be optionally substituted with one or more of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, OH, (CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, O(CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, CO<sub>2</sub>R<sup>6</sup>, CF<sub>3</sub>, or halogen; and two C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy groups may be combined to form a 5-7 membered ring, saturated or unsaturated, fused onto the Het ring. Preferred optional  
 10 substituents on Het are C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>mercaptyl, halogen, CF<sub>3</sub>, OCF<sub>3</sub>, CN, or NR<sup>4</sup>R<sup>5</sup>.

Het' is defined as for Het and may be optionally substituted by one or more of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, OH, (CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, O(CH<sub>2</sub>)<sub>1-6</sub>NR<sup>4</sup>R<sup>5</sup>, CO<sub>2</sub>R<sup>6</sup>, CF<sub>3</sub>, or halogen.

15 Examples of such heterocycles include, but are not limited to piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidinyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridinyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl,  
 20 thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furyl, pyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzoxazolyl, benzofuranyl, benzothiophenyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl, as well as triazolyl, thiadiazolyl, oxadiazolyl, isoxazolyl, isothiazolyl, imidazolyl,  
 25 pyridazinyl, pyrimidinyl and triazinyl which are available by routine chemical synthesis and are stable.

Compounds of this invention of formula (I), do not include compounds wherein R<sup>2</sup> is optionally substituted Het-C<sub>0</sub>alkyl, and Het is indole, benzofuran, benzothiophene, benzisoxazole, benzothiozole or benzopyrazole,  
 30 and the optional substituent is -(CH<sub>2</sub>)<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>. The following compounds of this invention are known: 3-(4-methyl-anilino)-5-benzylthio-1,2,4-triazole, 3-(2-methyl-anilino)-5-benzylthio-1,2,4-triazole, 3-(4-methoxy-anilino)-5-benzylthio-1,2,4-triazole, 3-(2-methoxy-anilino)-5-benzylthio-1,2,4-triazole, or 3-ethyl-3-anilino-5-benzylthio-1,2,4-triazole. Fromm et al., *Justus Liebigs Ann. Chem.*, 437 1924, 113. A compound of formula (I) wherein R<sup>1</sup> is benzyl,  
 35 R<sup>2</sup> is phenyl and R<sup>3</sup> is hydrogen is known.



Suitably, when moieties R<sup>1</sup>, R<sup>2</sup>, or R<sup>3</sup> are either optionally substituted Ar-C<sub>0-6</sub>alkyl or optionally substituted Het-C<sub>0-6</sub>alkyl, the moiety may be attached to the triazole substituent through the aromatic ring or through the alkyl chain.

5 Further, it will be understood that when a moiety is "optionally substituted" the moiety may have one or more optional substituents, each optional substituent being independently selected.

The terms "hetero" or "heteroatom" as used herein interchangeably at all occurrences mean oxygen, nitrogen and sulfur.

10 The terms "halo" or "halogen" as used herein interchangeably at all occurrences mean F, Cl, Br, and I.

Here and throughout this application the term C<sub>0</sub> denotes the absence of the substituent group immediately following; for instance, in the moiety ArC<sub>0-6</sub>alkyl, when C is 0, the substituent is Ar, e.g., phenyl. Conversely,  
15 when the moiety ArC<sub>0-6</sub>alkyl is identified as a specific aromatic group, e.g., phenyl, it is understood that C is 0.

Suitably X is sulfur or oxygen. Preferably X is sulfur.

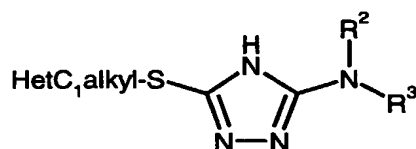
Suitably, R<sup>1</sup> is optionally substituted C<sub>2-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, or C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl. Preferably R<sup>1</sup> is optionally substituted  
20 Ar-C<sub>0-6</sub>alkyl or optionally substituted Het-C<sub>0-6</sub>alkyl. More preferably R<sup>1</sup> is optionally substituted Ar-C<sub>1</sub>alkyl or optionally substituted Het-C<sub>1</sub>alkyl. Most preferably R<sup>1</sup> is optionally substituted benzyl, optionally substituted methylfuran or optionally substituted methylthiophene. Preferably, when R<sup>1</sup>  
25 is Het-C<sub>1</sub>alkyl, the alkyl chain is directly attached to moiety X.

Suitably, R<sup>2</sup> is optionally substituted C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl. Preferably, R<sup>2</sup> is optionally substituted Ar-C<sub>0-6</sub>alkyl. More preferably R<sup>2</sup> is optionally substituted Ar-C<sub>0</sub>alkyl. Most  
30 preferably R<sup>2</sup> is optionally substituted Ar-C<sub>0</sub>alkyl, wherein the optional substituent is ortho C<sub>1-6</sub>alkyl, preferably branched C<sub>1-6</sub>alkyl, most preferably isopropyl.

Suitably, R<sup>3</sup> is H, optionally substituted C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl, optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, or C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl, C<sub>0-6</sub>alkyl-C(O)X'AB, C<sub>0-6</sub>alkyl-S(O)<sub>2</sub>X'AB, C<sub>0-6</sub>alkyl-X'AB, wherein X' is O, S, C or N; A and B are  
35 independently H, optionally substituted C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyl, C<sub>3-6</sub>alkynyl,

optionally substituted Ar-C<sub>0-6</sub>alkyl, optionally substituted Het-C<sub>0-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl, or A or B are independently absent. Preferably R<sup>3</sup> is hydrogen or C<sub>0-6</sub>alkyl-C(O)X'AB. More preferably R<sup>3</sup> is hydrogen or C<sub>0-6</sub>alkyl-C(O)X'AB, wherein X' is oxygen and A is methyl or hydrogen and B is absent.

A preferred compound of this invention is a compound of formula (IB):



Formula (IB).

Suitably, pharmaceutically acceptable salts of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, and stearate.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The stereocenters may be (R), (S) or any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R). All of these compounds are within the scope of the present invention.

All compounds of formula (IA) specifically named herein are considered to be part of the invention disclosed herein. Among the compounds of the invention of formula (IA) are the following compounds:

- 3-anilino-5-benzylthio-1,2,4-triazole;
- 3-anilino-5-methylthio-1,2,4-triazole;
- 3-anilino-5-(4-chloro-benzylthio)-1,2,4-triazole;
- 3-anilino-5-allylthio-1,2,4-triazole;
- 3-anilino-5-(2-methyl-2-butenylthio)-1,2,4-triazole;
- 3-anilino-5-(2-methyl-butylthio)-1,2,4-triazole;
- 3-anilino-5-(2-methyl-2-pentenylthio)-1,2,4-triazole;
- 3-anilino-5-( $\alpha$ -methylbenzylthio)-1,2,4-triazole;
- 3-anilino-5-(cyclohexylmethylthio)-1,2,4-triazole;
- 3-anilino-5-(propyl acetylthio)-1,2,4-triazole;

- 3-anilino-5-(3,3-dimethoxy-propylthio)-1,2,4-triazole;  
3-anilino-5-(2-phenethylthio)-1,2,4-triazole;  
3-anilino-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
3-anilino-5-(3-phenyl-[1,2,4]oxadiazol-5-ylmethylthio)-1,2,4-triazole;  
5 3-anilino-5-(1*H*-benzoimidazol-2-ylmethylthio)-1,2,4-triazole;  
3-anilino-5-(2-(4-chlorophenyl)-thiazol-4-ylmethylthio)-1,2,4-triazole;  
3-anilino-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole;  
3-anilino-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;  
3-anilino-5-(4-*i*-propyl-benzylthio)-1,2,4-triazole;  
10 3-anilino-5-(pyridin-4-ylmethylthio)-1,2,4-triazole;  
3-anilino-5-(quinolin-8-ylthio)-1,2,4-triazole;  
3-anilino-5-(4-acetamido-benzylthio)-1,2,4-triazole;  
4-(5-anilino-2 *H*-[1,2,4]triazol-3-yl thio)-benzoic acid;  
3-anilino-5-(2-methyl-benzylthio)-1,2,4-triazole;  
15 3-anilino-5-(4-trifluoromethyl-benzylthio)-1,2,4-triazole;  
3-anilino-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-anilino-5-(3,5-dimethyl-benzylthio)-1,2,4-triazole;  
3-anilino-5-(4-cyano-benzylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;  
20 3-(4-methyl-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;  
25 3-(4-methyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
30 3-(4-methyl-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
35 3-(2-methyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;

- 3-(2-methyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;  
3-(4-chloro-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;  
5 3-(4-chloro-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole;  
3-(4-chloro-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;  
3-(4-chloro-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(4-chloro-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
3-(4-chloro-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;  
10 3-(4-chloro-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(4-chloro-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
3-(4-chloro-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole;  
3-(4-chloro-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;  
15 3-(4-methoxy-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;  
20 3-(4-methoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;  
4-(5-(cyclohexylmethylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid  
25 methyl ester;  
4-(5-(pyridin-4-ylmethylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid  
methyl ester;  
4-(5-(2-methyl-2-butenylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid  
methyl ester;  
30 4-(5-(2-fluoro-benzylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl  
ester;  
4-(5-(5-methyl-isoxazol-3-ylmethylthio)-1H-[1,2,4]triazol-3-ylamino)-  
benzoic acid methyl ester;  
4-(5-(3-methoxy-benzylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid  
35 methyl ester;  
4-(5-(2-methyl-benzylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl  
ester;

- 4-(5-(3,4-difluoro-benzylthio)-1*H*-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester;
- 4-(5-(2-methoxy-benzylthio)-1*H*-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester;
- 5 4-(5-(2-methyl-thiazol-4-ylmethylthio)-1*H*-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester;
- 4-(5-(pyridin-2-ylmethylthio)-1*H*-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester;
- 3-(3,4-dimethoxy-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;
- 10 3-(3,4-dimethoxy-anilino)-5-(3-methoxy-benzylthio)-1,2,4-triazole;
- 3-(3,4-dimethoxy-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;
- 3-(3,4-dimethoxy-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole;
- 3-(3,4-dimethoxy-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;
- 3-(3,4-dimethoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;
- 15 3-(3,4-dimethoxy-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;
- 3-(3,4-dimethoxy-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;
- 3-(3,4-dimethoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;
- 3-(3,4-dimethoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;
- 20 3-(3,4-dimethoxy-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole;
- 3-(3,4-dimethoxy-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;
- 3-(2-phenyl-anilino)-5-benzylthio-1,2,4-triazole;
- 3-(2-phenyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;
- 3-(2-phenyl-anilino)-5-(3-methoxy-benzylthio)-1,2,4-triazole;
- 25 3-(2-phenyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;
- 3-(2-phenyl-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole;
- 3-(2-phenyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;
- 3-(2-phenyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;
- 3-(2-phenyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;
- 30 3-(2-phenyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;
- 3-(2-phenyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;
- 3-(2-phenyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;
- 3-(2-phenyl-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole;
- [5-(benzylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;
- 35 [5-(3-methoxybenzylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;
- [5-(cyclohexylmethylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;
- [5-(pyridin-4-ylmethylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;

[5-(2-methyl-2-butenylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
 [5-(2-fluoro-benzylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
 [5-(5-methyl-isoxazol-3-ylmethylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;

- 5     [5-(2-methyl-benzylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
       [5-(3,4-difluoro-benzylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
       [5-(2-methoxy-benzylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
       [5-(pyridin-2-ylmethylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
       [5-(2-methyl-thiazol-4-ylmethylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-
- 10    amine;  
       [5-(thiophen-2-ylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
       3-(2-ethyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
       3-(2-ethyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
       3-(2-ethyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;
- 15    3-(2-ethyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
       3-(2-ethyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;  
       3-(2-ethyl-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole;  
       3-(2-ethyl-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole;  
       3-(2-ethyl-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole;
- 20    3-(2-ethyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
       3-(2-ethyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;  
       3-(2-ethyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
       3-(2-methoxy-anilino)-5-benzylthio-1,2,4-triazole;  
       3-(2-methoxy-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;
- 25    3-(2-methoxy-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;  
       3-(2-methoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
       3-(2-methoxy-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;  
       3-(2-methoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
       3-(2-methoxy-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;
- 30    3-(2-methoxy-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole;  
       3-(2-methoxy-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole;  
       3-(2-methoxy-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole;  
       3-(2-methoxy-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
       3-(2-methoxy-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;
- 35    3-(2-methoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
       3-(2-isopropyl-anilino)-5-benzylthio-1,2,4-triazole;  
       3-(2-isopropyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;

- 3-(2-isopropyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
5 3-(2-isopropyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
10 3-(2-isopropyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
15 3-(3-methyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole;  
20 3-(3-methyl-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
25 3-(4-*n*-butyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole;  
30 3-(4-*n*-butyl-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
35 3-(2,4-dimethoxy-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
3-(2,4-dimethoxy-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;  
3-(2,4-dimethoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;

- 3-(2,4-dimethoxy-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;  
3-(2,4-dimethoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(2,4-dimethoxy-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;  
3-(2,4-dimethoxy-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole;  
5 3-(2,4-dimethoxy-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole;  
3-(2,4-dimethoxy-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole;  
3-(2,4-dimethoxy-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
3-(2,4-dimethoxy-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;  
10 3-(2,4-dimethoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;  
15 3-(2-methyl-4-methoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole;  
20 3-(2-methyl-4-methoxy-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
25 3-(2,6-dimethyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
3-(2,6-dimethyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole;  
3-(2,6-dimethyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(2,6-dimethyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole;  
3-(2,6-dimethyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
30 3-(2,6-dimethyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole;  
3-(2,6-dimethyl-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole;  
3-methyl-3-anilino-5-benzylthio-1,2,4-triazole;  
3-ethyl-3-anilino-5-benzylthio-1,2,4-triazole;  
3-*n*-propyl-3-anilino-5-benzylthio-1,2,4-triazole;  
35 3-*n*-butyl -3-anilino-5-benzylthio-1,2,4-triazole;  
3-*i*-propyl -3-anilino-5-benzylthio-1,2,4-triazole;  
3-allyl-3-anilino-5-benzylthio-1,2,4-triazole; and



3-benzyl-3-anilino-5-benzylthio-1,2,4-triazole.

Among the preferred compounds of formula (IA) of this invention are the following compounds:

- 5 3-anilino-5-benzylthio-1,2,4-triazole;  
3-(4-methyl-anilino)-5-benzylthio-1,2,4-triazole;  
3-(2-methyl-anilino)-5-benzylthio-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-benzylthio-1,2,4-triazole;  
3-(2-methoxy-anilino)-5-benzylthio-1,2,4-triazole;
- 10 3-ethyl-3-anilino-5-benzylthio-1,2,4-triazole;  
3-(4-chloro-anilino)-5-benzylthio-1,2,4-triazole;  
3-(3,4-dimethoxy-anilino)-5-benzylthio-1,2,4-triazole;  
3-(2-ethyl-anilino)-5-benzylthio-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-benzylthio-1,2,4-triazole;
- 15 3-(3-methyl-anilino)-5-benzylthio-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-benzylthio-1,2,4-triazole;  
3-(2,4-dimethoxy-anilino)-5-benzylthio-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-benzylthio-1,2,4-triazole;  
3-(2,6-dimethyl-anilino)-5-benzylthio-1,2,4-triazole;
- 20 3-methylacetate-3-(*p*-methyl)-anilino-5-benzylthio-1,2,4-triazole;  
3-methylacetate-3-(*p*-methoxy)-anilino-5-benzylthio-1,2,4-triazole;  
3-methylacetate-3-(2,6-dimethyl)-anilino-5-benzylthio-1,2,4-triazole;  
3-anilino-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
3-anilino-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole;
- 25 5-(5-phenylamino-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carboxylic acid ethyl ester;  
5-(5-phenylamino-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carbaldehyde;  
3-(4-methyl-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole;
- 30 3-(4-methyl-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
5-(5-*p*-tolyl amino-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carboxylic acid ethyl ester;
- 35 3-(4-methyl-anilino)-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole;  
5-(5-*p*-tolyl amino-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carbaldehyde;

- 3-(2-methyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
5 3-(2-methyl-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
5-(5-*o*-tolyl amino-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carboxylic  
acid ethyl ester;  
3-(2-methyl-anilino)-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole;  
5-(5-*o*-tolyl amino-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-  
10 carbaldehyde;  
3-(2-methyl-anilino)-5-(furan-3-ylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
3-(3,4-dimethoxy-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
15 [5-(thiophen-2-ylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
3-(2-ethyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-methoxy-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-methoxy-anilino)-5-(furan-2-ylthio)-1,2,4-triazole;  
5-(5-(2-methoxyphenylamino)-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-  
20 carboxylic acid ethyl ester  
3-(2-methoxy-anilino)-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-methoxy-anilino)-5-(thiophen-3-ylthio)-1,2,4-triazole;  
3-(2-methoxy-anilino)-5-(furan-3-ylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
25 3-(3-methyl-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
5-(5-(3-methylphenylamino)-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-  
30 carboxylic acid ethyl ester;  
3-(3-methyl-anilino)-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole;  
5-(5-(3-methylphenylamino)-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-  
carbaldehyde;  
3-(4-*n*-butyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
35 3-(2,4-dimethoxy-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
3-(4-fluoro-anilino)-5-(furan-2-ylthio)-1,2,4-triazole;

- 3-(4-fluoro-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
3-(4-fluoro-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
3-(4-fluoro-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
3-(4-fluoro-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
5 5-(5-(4-fluorophenylamino)-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carboxylic acid ethyl ester;  
3-(4-fluoro-anilino)-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole;  
5-(5-(4-fluorophenylamino)-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carbaldehyde;  
10 3-anilino-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(2-methyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(4-chloro-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
15 3-(2-methyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(4-chloro-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
20 4-(5-(3-methoxy-benzylthio)-1*H*-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester;  
4-(5-(3,4-difluoro-benzylthio)-1*H*-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester;  
4-(5-(2-methoxy-benzylthio)-1*H*-[1,2,4]triazol-3-ylamino)-benzoic acid  
25 methyl ester;  
3-(3,4-dimethoxy-anilino)-5-(3-methoxy-benzylthio)-1,2,4-triazole;  
3-(3,4-dimethoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(3,4-dimethoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(3,4-dimethoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole;  
30 [5-(2-fluoro-benzylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
[5-(3,4-difluoro-benzylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
[5-(2-methoxy-benzylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
[5-(thiophen-2-ylthio)-1*H*-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine;  
3-(2-ethyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
35 3-(2-ethyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
3-(2-ethyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(2-methoxy-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;

- 3-(2-methoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(2-methoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
5 3-(3-methyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(4-*n*-butyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(2,4-dimethoxy-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
10 3-(2,4-dimethoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(2,4-dimethoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(2-methyl-4-methoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
15 3-(2,6-dimethyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole;  
3-(2,6-dimethyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole;  
3-(2,6-dimethyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole;  
3-(4-fluoro-anilino)-5-(thiophen-3-ylthio)-1,2,4-triazole; and  
3-(4-fluoro-anilino)-5-(furan-3-ylthio)-1,2,4-triazole.

20

Among the more preferred compounds of formula (IA) are the following compounds:

- 3-(4-methyl-anilino)-5-benzylthio-1,2,4-triazole;  
3-(2-methyl-anilino)-5-benzylthio-1,2,4-triazole;  
25 3-(4-methoxy-anilino)-5-benzylthio-1,2,4-triazole;  
3-methylacetate-3-anilino-5-benzylthio-1,2,4-triazole;  
4-(5-benzylthio-1*H*-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester;  
3-anilino-5-(thiophen-2-ylthio)-1,2,4-triazole;  
3-anilino-5-(furan-3-ylthio)-1,2,4-triazole;  
30 3-anilino-5-(furan-2-ylthio)-1,2,4-triazole;  
3-anilino-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
3-anilino-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
3-anilino-5-(thiophen-3-ylthio)-1,2,4-triazole;  
3-anilino-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole;  
35 3-(4-methyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(thiophen-3-ylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole;

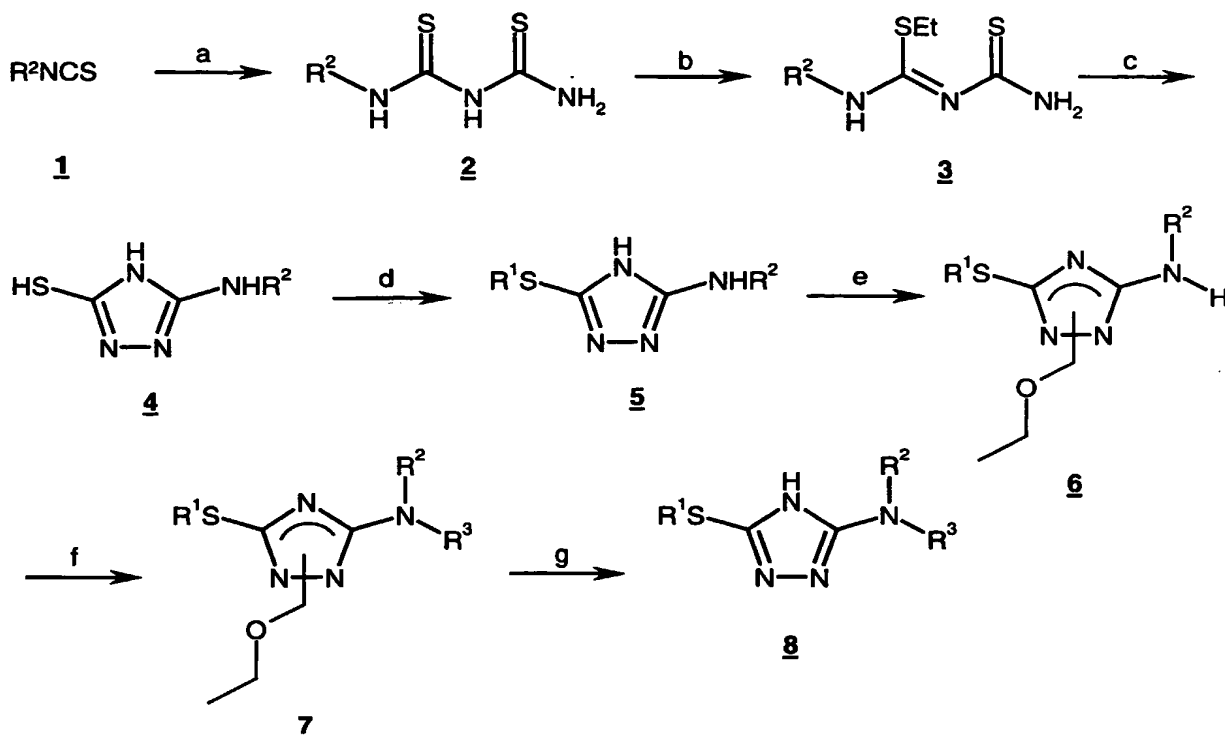
- 3-(2-methyl-anilino)-5-(furan-2-ylthio)-1,2,4-triazole;  
3-(4-chloro-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
3-(4-methoxy-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-methoxy-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
5 3-(2-methoxy-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(furan-2-ylthio)-1,2,4-triazole;  
3-(3-methyl-anilino)-5-(furan-3-ylthio)-1,2,4-triazole; and  
3-(3-methyl-anilino)-5-(thiophen-3-ylthio)-1,2,4-triazole.

- 10 Among the most preferred compounds of formula (IA) are the following compounds:  
3-(2-isopropyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(furan-2-ylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
15 3-(2-isopropyl-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole;  
5-(5-(2-isopropylphenylamino)-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carboxylic acid ethyl ester;  
20 5-(5-(2-isopropyl amino)-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carbaldehyde;  
3-(2-isopropyl-anilino)-5-(thiophen-3-ylthio)-1,2,4-triazole;  
3-(2-isopropyl-anilino)-5-(furan-3-ylthio)-1,2,4-triazole;  
3-(4-methyl-anilino)-5-(furan-2-ylthio)-1,2,4-triazole;  
25 3-(4-methyl-anilino)-5-(furan-3-ylthio)-1,2,4-triazole;  
3-(2-methoxy-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole; and  
3-(2-methoxy-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole.

#### Methods of Preparation

- 30 Compounds of the formulae (I) and (IA) wherein X is S and R<sup>3</sup> is H, were prepared by methods analogous to those described in Scheme 1.

Scheme 1

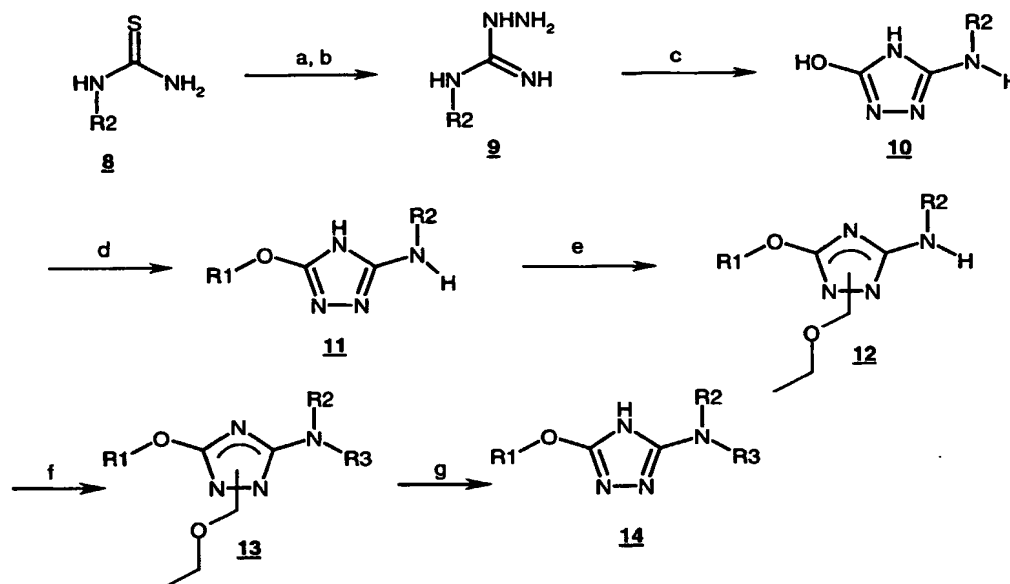


- 5 a) Thiourea, NaOH, H<sub>2</sub>O/CH<sub>3</sub>CN; b) EtI, Et<sub>3</sub>N, DMF; c) H<sub>2</sub>NNH<sub>2</sub>, EtOH; d)  
 R<sup>1</sup>X (X = halogen), K<sub>2</sub>CO<sub>3</sub>, DMF; e) ClCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, NaH, THF; f)  
 R<sup>3</sup>CH<sub>2</sub>Br, NaH, DMF; g) TFA.

An isothiocyanate (such as phenyl isothiocyanate) (1-Scheme 1) was treated with thiourea and sodium hydroxide in acetonitrile/water to provide 2-Scheme 1, which was treated with iodoethane and triethylamine in DMF to afford 3-Scheme 1. Treatment of 3-Scheme 1 with hydrazine in ethanol provided 4-Scheme 1, which was treated with an alkyl halide (such as benzyl bromide or 4-chlorobenzyl chloride) and potassium carbonate in DMF to give 5-Scheme 1. Triazole 5-Scheme 1 is protected as the methoxy methylethyl ether to afford 6-Scheme 1. Alkylation of 6-Scheme 1 with an alkyl halide (such as methyl iodide, ethyl iodide, *i*-isobutyl iodide, *n*-propyl iodide, butyl iodide, allyl bromide, benzyl bromide, and methyl bromoacetate) afforded the desired tertiary amine 7-Scheme 1. Deprotection of the MOM-ether 7-Scheme 1 with trifluoroacetic acid (TFA) provided the desired product 8-Scheme 1.

Compounds of the formulae (I) and (IA) wherein X is O may be prepared by methods analogous to those described in Scheme 2.

## Scheme 2



- a) Thiourea, EtI, EtOH; b)  $\text{NH}_2\text{NH}_2$ , EtOH c) 1,1'-Carbonyldiimidazole, EtOH; d)  $\text{R}^1\text{X}$  (X = halogen),  $\text{K}_2\text{CO}_3$ , DMF; e)  $\text{ClCH}_2\text{OCH}_2\text{CH}_3$ , NaH, THF; f)  $\text{R}^3\text{CH}_2\text{Br}$ , NaH, DMF; g) TFA.

A thiourea (such as phenylthiourea) (8-Scheme 2) may be treated with ethyl iodide and refluxed in EtOH, and the resulting *S*-ethyl thiourea is then heated in the presence of hydrazine to provide 9-Scheme 2. The hydrazine 9-Scheme 2 is treated with carbonyldiimidazole and heated to afford 10-Scheme 2. Treatment of 10-Scheme 2 with an alkyl halide (such as benzyl bromide or 4-chlorobenzyl chloride) and potassium carbonate in DMF gives 11-Scheme 2. Triazole 11-Scheme 2 is protected as the methoxy methylethyl ether to afford 12-Scheme 2. Alkylation of 12-Scheme 2 with an alkyl halide (such as methyl iodide, ethyl iodide, *i*-isobutyl iodide, *n*-propyl iodide, butyl iodide, allyl bromide, benzyl bromide, and methyl bromoacetate) affords the desired tertiary amine 13-Scheme 2. Deprotection of the MOM-ether 13-Scheme 2 with trifluoroacetic acid (TFA) provides the desired product 14-Scheme 2.

## Formulation of Pharmaceutical Compositions

The pharmaceutically effective compounds of this invention (and the pharmaceutically acceptable salts thereof) are administered in conventional dosage forms prepared by combining a compound of this invention ("active ingredient") in an amount sufficient to treat cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic

neovascularization, psoriasis, ocular neovascularization or obesity ("MetAp2-mediated disease states") with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1000 mg. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The active ingredient may also be administered topically to a mammal in need of treatment or prophylaxis of MetAP2-mediated disease states. The amount of active ingredient required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the disease state being treated and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of the active ingredient externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to



10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and  
5 for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-  
10 liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active  
15 ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the  
20 solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol  
25 and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods  
30 similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be  
35 made by mixing the active ingredient in finely divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise

hydrocarbons such as hard; soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol. The formulation may  
5 incorporate any suitable surface-active agent such as an anionic, cationic or non-ionic surfactant such as esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

10 The active ingredient may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of the active ingredient administered by inhalation is from about  
15 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

In one aspect, this invention relates to a method of treating cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization or obesity, all in mammals, preferably humans, which comprises administering to such  
20 mammal an effective amount of a MetAP2 inhibitor, in particular, a compound of this invention.

By the term "treating" is meant either prophylactic or therapeutic therapy. Such compound can be administered to such mammal in a conventional dosage form prepared by combining the compound of this  
25 invention with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The  
30 compound is administered to a mammal in need of treatment for cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization or obesity, in an amount sufficient to decrease symptoms associated with these disease states. The route of administration may be oral or parenteral.

35 The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are

generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

5 It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of this invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will  
10 also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

## 15 EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In the Examples, proton NMR spectra were performed upon a Bruker 400 MHz NMR spectrometer, unless  
20 otherwise indicated.

### Example 1

#### Preparation of 3-anilino-5-benzylthio-1,2,4-triazole

##### a) 1-Phenyl-2,4-dithiobiuret

To a stirring solution of NaOH (0.52 g, 13.1 mmol) in 60 mL of 10%  
25 H<sub>2</sub>O:CH<sub>3</sub>CN was added thiourea (1.0 g, 13.1 mmol). The resulting suspension was heated to 40 °C for 20 min. and then cooled to RT. To this mixture was added phenylisothiocyanate (1.5 ml, 13.1 mmol), and the clear yellow solution was stirred overnight. After stirring for 12 h, 1 N HCl was added until a white precipitate formed. The precipitate was filtered, washed with H<sub>2</sub>O, and dried  
30 under vacuum to produce the title compound as a light yellow powder (0.78 g, 30%). <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ7.25 (t, 2H, J=7.3 Hz), 7.40 (t, 2H, J=7.9 Hz), 7.56 (d, 1H, J=7.9 Hz), 9.13-9.29 (broad singlet, 1H), and 10.26-10.79 (broad singlet, 2H).

##### b) 2-Ethyl-1-phenyl-2-isodithiobiuret

35 To a stirring solution of the compound of Example 1(a) (150 mg, 0.70 mmol) in 4 mL of DMF was added triethylamine (57 uL, 0.70 mmol). The resulting yellow/green solution was stirred for 10 min at RT. To this solution

was added ethyl iodide (100 uL, 0.70 mmol), and the reaction mixture was stirred for 2 h at RT. The yellow solution was poured into 20 mL of H<sub>2</sub>O and extracted four times with EtOAc. The organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated, and the crude residue was subjected to column chromatography (silica gel; ethyl acetate/hexane) to afford the title compound as a white crystalline solid (108 mg, 64%). <sup>1</sup>H-NMR (400MHz, d<sub>6</sub>-DMSO) δ 1.22 (t, 3H, J=7.2 Hz), 2.96 (quartet, 2H, J=7.2 Hz), 6.85 (d, 1H, J=7.6 Hz), 7.16 (t, 1H, J=7.2 Hz), 7.29-7.41 (m, 3H), 8.27 (broad singlet, 1H), 9.89 (broad singlet, 1H), and 10.99 (broad singlet, 1H).

c) 3-anilino-5-mercapto-1,2,4-triazole

To a stirring solution of the compound of Example 1(b) in 2 mL of EtOH was added 50 uL of anhydrous hydrazine. The reaction mixture was heated at 80 °C for 1 h, concentrated to dryness, and then purified by preparative HPLC to yield the title compound as a white solid (30 mg, 37%). MS (ESI) 190.90 (M-H)<sup>+</sup>.

d) 3-anilino-5-benzylthio-1,2,4-triazole

To a stirring solution of the compound of Example 1(c) (23 mg, 0.12 mmol) in 1.2 mL of DMF was added K<sub>2</sub>CO<sub>3</sub> (17 mg, 0.12 mmol), followed by benzyl bromide (20 mg, 0.12 mmol). The mixture was stirred overnight, filtered, and purified by preparative HPLC to afford the title compound as a white solid (30 mg, 70%). <sup>1</sup>H-NMR (400MHz, d<sub>6</sub>-DMSO) δ 9.30 (broad singlet, 1H), 7.47 (d, 2H, J=8.1 Hz), 7.39 (d, 2H, J=7.3 Hz), 7.31 (t, 2H, J=7.3 Hz), 7.23 (quartet, 3H, J=7.3 Hz), 6.82 (t, 1H, J=7.3 Hz), and 4.3 (s, 2H).

Example 2

Preparation of 3-anilino-5-(4-chlorobenzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except substituting 4-chlorobenzyl bromide for benzyl bromide in step 1(d), the title compound was prepared as a white solid. <sup>1</sup>H-NMR (400MHz, d<sub>6</sub>-DMSO) δ 9.32 (broad singlet, 1H), 7.46 (d, 2H, J=7.8 Hz), 7.41 (d, 2H, J=8.4 Hz), 7.36 (d, 2H, J=8.4 Hz), 7.22 (t, 2H, J=7.8 Hz), 6.82 (t, 1H, J=7.24 Hz), and 4.33 (s, 2H).

Example 3

Preparation of 3-anilino-5-methylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except methyl iodide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 413.2 (2M+H)<sup>+</sup>.

#### Example 4

##### Preparation of 3-anilino-5-allylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except allyl bromide  
5 was substituted for benzyl bromide in step 1(d), the title compound was  
prepared as a white solid. MS (ESI) 233.0 (M+H)<sup>+</sup>.

#### Example 5

##### Preparation of 3-anilino-5-(2-methyl-2-butenylthio)-1,2,4-triazole

10 Following the procedure of Example 1(a)-1(d), except 1-bromo-3-  
methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title  
compound was prepared as a white solid. MS (ESI) 261.2 (M+H)<sup>+</sup>.

#### Example 6

##### Preparation of 3-anilino-5-(2-methyl-butylthio)-1,2,4-triazole

15 Following the procedure of Example 1(a)-1(d), except 1-bromo-3-  
methylbutane was substituted for benzyl bromide in step 1(d), the title  
compound was prepared as a white solid. MS (ESI) 263.2 (M+H)<sup>+</sup>.

#### Example 7

##### Preparation of 3-anilino-5-(2-methyl-2-pentenylthio)-1,2,4-triazole

20 Following the procedure of Example 1(a)-1(d), except 5-bromo-2-  
methyl-2-pentene was substituted for benzyl bromide in step 1(d), the title  
compound was prepared as a white solid. MS (ESI) 275.2 (M+H)<sup>+</sup>.

#### Example 8

##### Preparation of 3-anilino-5-( $\alpha$ -methylbenzylthio)-1,2,4-triazole

25 Following the procedure of Example 1(a)-1(d), except (1-bromoethyl)  
benzene was substituted for benzyl bromide in step 1(d), the title compound  
30 was prepared as a white solid. MS (ESI) 297.2 (M+H)<sup>+</sup>.

#### Example 9

##### Preparation of 3-anilino-5-(cyclohexylmethylthio)-1,2,4-triazole

35 Following the procedure of Example 1(a)-1(d), except  
bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the  
title compound was prepared as a white solid. MS (ESI) 289.0 (M+H)<sup>+</sup>.

### Example 10

#### Preparation of 3-anilino-5-(propyl acetylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except propyl bromoacetate was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 293.2 (M+H)<sup>+</sup>.

### Example 11

#### Preparation of 3-anilino-5-(3,3-dimethoxy-propylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3-bromo-1,1-dimethoxy-propane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 295.2 (M+H)<sup>+</sup>.

### Example 12

#### Preparation of 3-anilino-5-(2-phenethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except (2-bromoethyl)benzene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 297.2 (M+H)<sup>+</sup>.

### Example 13

#### Preparation of 3-anilino-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 288.2 (M+H)<sup>+</sup>.

### Example 14

#### Preparation of 3-anilino-5-(3-phenyl-[1,2,4]oxadiazol-5-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3-chloromethyl-5-phenyl-1,2,4-oxadiazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 351.2 (M+H)<sup>+</sup>.

### Example 15

#### Preparation of 3-anilino-5-(1H-benzimidazol-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-(chloromethyl)-benzimidazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 323.2 (M+H)<sup>+</sup>.

Example 16Preparation of 3-anilino-5-(2-(4-chlorophenyl)-thiazol-4-ylmethylthio)-1,2,4-triazole

5        Following the procedure of Example 1(a)-1(d), except 4-chloromethyl-2-(4-chlorophenyl)thiazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 400.0 (M+H)<sup>+</sup>.

Example 17

10    Preparation of 3-anilino-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-chloromethyl-2-methylthiazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 304.2 (M+H)<sup>+</sup>.

Example 18

15    Preparation of 3-anilino-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 284.2 (M+H)<sup>+</sup>.

Example 19

20    Preparation of 3-anilino-5-(pyridin-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 284.0 (M+H)<sup>+</sup>.

Example 20

30    Preparation of 3-anilino-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-chloromethylthiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 289.0 (M+H)<sup>+</sup>.

Example 21

35    Preparation of 3-anilino-5-(4-*i*-propyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-isopropylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 325.2 (M+H)<sup>+</sup>.

Example 22Preparation of 3-anilino-5-(quinolin-8-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 8-bromomethylquinoline was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 334.2 (M+H)<sup>+</sup>.

Example 23Preparation of 3-anilino-5-(4-acetamido-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-acetamidobenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 340.2 (M+H)<sup>+</sup>.

Example 24Preparation of 4-(5-anilino-2 H-[1,2,4]triazol-3-yl thio)-benzoic acid

Following the procedure of Example 1(a)-1(d), except 4-(chloromethyl)benzoic acid was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 327.2 (M+H)<sup>+</sup>.

Example 25Preparation of 3-anilino-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 297.0 (M+H)<sup>+</sup>.

Example 26Preparation of 3-anilino-5-(4-trifluoromethyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-(trifluoromethyl)benzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 350.8 (M+H)<sup>+</sup>.

Example 27Preparation of 3-anilino-5-(3,5-dimethyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,5-dimethylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 311.4 (M+H)<sup>+</sup>.



### Example 28

#### Preparation of 3-anilino-5-(4-cyano-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-cyanobenzyl  
5 bromide was substituted for benzyl bromide in step 1(d), the title compound  
was prepared as a white solid. MS (ESI) 308.2 (M+H)<sup>+</sup>.

### Example 29

#### Preparation of 3-anilino-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

10 Following the procedure of Example 1(a)-1(d), except 3,4-  
difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title  
compound was prepared as a white solid. MS (ESI) 319.0 (M+H)<sup>+</sup>.

### Example 30

#### Preparation of 3-anilino-5-(furan-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-chloromethyl-  
furan (Berry, J. M.; Watson, C. Y.; Whish, W. J. D.; Threadgill, M. D. J.  
*Chem. Soc. Perkin Trans. 1* **1997**, 8, 1147) was substituted for benzyl bromide  
in step 1(d), the title compound was prepared as a white solid. MS (ESI)  
20 273.2 (M+H)<sup>+</sup>.

### Example 31

#### Preparation of 3-anilino-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-chloromethyl-  
25 3-methyl-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R.  
*C. Tetrahedron Lett.* **1988**, 29(1), 117) was substituted for benzyl bromide in  
step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2  
(M+H)<sup>+</sup>.

### Example 32

#### Preparation of 3-anilino-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-chloromethyl-  
3-chloro-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R.  
*C. Tetrahedron Lett.* **1988**, 29(1), 117) was substituted for benzyl bromide in  
35 step 1(d), the title compound was prepared as a white solid. MS (ESI) 323.2  
(M+H)<sup>+</sup>.

### Example 33

#### Preparation of 3-anilino-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-chloromethyl-5-methyl-thiophene (Moradpour, A. *J. Chem. Soc. Perkin Trans. 1*, **1993**, 1, 7) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

### Example 34

#### Preparation of 3-anilino-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-chloromethyl-5-chloro-thiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 323.0 (M+H)<sup>+</sup>.

### Example 35

#### Preparation of 5-(5-phenylamino-4H-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carboxylic acid ethyl ester

Following the procedure of Example 1(a)-1(d), except 5-chloromethyl-furan-2-carboxylic acid ethyl ester was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 345.2 (M)<sup>+</sup>.

### Example 36

#### Preparation of 3-anilino-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-chloromethyl-5-bromo-thiophene (Clapp, R. C.; Clark, J. H.; Vaughan, J. R.; English, J. P.; Anderson, G. W. *J. Am. Chem. Soc.* **1947**, 60, 1549) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 367.0 (M)<sup>+</sup>.

### Example 37

#### Preparation of 5-(5-phenylamino-4H-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carbaldehyde

Following the procedure of Example 1(a)-1(d), except 5-chloromethyl-furan-2-carbaldehyde (Sanda, K.; Rigal, L.; Delmas, M.; Gaset, A. *Synthesis* **1992**, 6, 541) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 301.2 (M+H)<sup>+</sup>.

### Example 38

#### Preparation of 3-anilino-5-(thiophen-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3-chloromethylthiophene (Lamy, J.; Lavit, D.; Buu-Hoi, N. P. *J. Chem. Soc.* **1958**, 4202) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 289.0 (M+H)<sup>+</sup>.

### Example 39

#### Preparation of 3-anilino-5-(furan-3-ylthio)-1,2,4-triazole ..

Following the procedure of Example 1(a)-1(d), except 3-chloromethylfuran (Arena, G.; Cali, R.; Maccarone, E.; Passerini, A. *J. Chem. Soc. Perkin Trans. 2* **1993**, 10, 1941) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 273.2 (M+H)<sup>+</sup>.

### Example 40

#### Preparation of 3-(4-methyl-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a), the title compound was prepared as a white solid. MS (ESI) 297.0 (M+H)<sup>+</sup>.

### Example 41

#### Preparation of 3-(4-methyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

### Example 42

#### Preparation of 3-(4-methyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.0 (M+H)<sup>+</sup>.

Example 43Preparation of 3-(4-methyl-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 298.2 (M+H)<sup>+</sup>.

Example 44Preparation of 3-(4-methyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 275.2 (M+H)<sup>+</sup>.

Example 45Preparation of 3-(4-methyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 315.0 (M+H)<sup>+</sup>.

Example 46Preparation of 3-(4-methyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 302.2 (M+H)<sup>+</sup>.

Example 47Preparation of 3-(4-methyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 311.2 (M+H)<sup>+</sup>.

Example 48Preparation of 3-(4-methyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 333.2 (M+H)<sup>+</sup>.

Example 49Preparation of 3-(4-methyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 327.2 (M+H)<sup>+</sup>.

Example 50Preparation of 3-(4-methyl-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-chloromethyl-2-methylthiazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 318.2 (M+H)<sup>+</sup>.

Example 51Preparation of 3-(4-methyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 298.2 (M+H)<sup>+</sup>.

Example 52Preparation of 3-(4-methyl-anilino)-5-(furan-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-furan (Berry, J. M.; Watson, C. Y.; Whish, W. J. D.; Threadgill, M. D. J. *Chem. Soc. Perkin Trans. 1* 1997, 8, 1147) was substituted for benzyl

bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 287.2 (M+H)<sup>+</sup>.

#### Example 53

5 Preparation of 3-(4-methyl-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-methyl-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* 1988, 29(1), 117) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 317.2 (M+H)<sup>+</sup>.

#### Example 54

15 Preparation of 3-(4-methyl-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-chloro-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* 1988, 29(1), 117) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 337.2 (M+H)<sup>+</sup>.

#### Example 55

25 Preparation of 3-(4-methyl-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-methyl-thiophene (Moradpour, A. J. *Chem. Soc. Perkin Trans. 1*, 1993, 1, 7) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 317.2 (M+H)<sup>+</sup>.

#### Example 56

35 Preparation of 3-(4-methyl-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-

chloromethyl-5-chloro-thiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 337.2 (M+H)<sup>+</sup>.

5

Example 57Preparation of 5-(5-*p*-tolyl amino-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carboxylic acid ethyl ester

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 5-chloromethyl-furan-2-carboxylic acid ethyl ester was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 359.2 (M+H)<sup>+</sup>.

15

Example 58Preparation of 3-(4-methyl-anilino)-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-bromo-thiophene (Clapp, R. C.; Clark, J. H; Vaughan, J. R.; English, J. P.; Anderson, G. W. *J. Am. Chem. Soc.* **1947**, *60*, 1549) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 381.0 (M)<sup>+</sup>.

25

Example 59Preparation of 5-(5-*p*-tolyl amino-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carbaldehyde

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 5-chloromethyl-furan-2-carbaldehyde (Sanda, K.; Rigal, L.; Delmas, M.; Gaset, A. *Synthesis* **1992**, *6*, 541) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 315.2 (M+H)<sup>+</sup>.

35

Example 60Preparation of 3-(4-methyl-anilino)-5-(thiophen-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-chloromethyl-thiophene (Lamy, J.; Lavit, D.; Buu-Hoi, N. P. *J. Chem. Soc.*

1958, 4202) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

#### Example 61

5 Preparation of 3-(4-methyl-anilino)-5-(furan-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-chloromethyl-furan (Arena, G.; Cali, R.; Maccarone, E.; Passerini, A. *J. Chem. Soc. Perkin Trans. 2* **1993**, 10, 1941) was substituted for benzyl bromide in  
10 step 1(d), the title compound was prepared as a white solid. MS (ESI) 287.2 (M+H)<sup>+</sup>.

#### Example 62

Preparation of 3-(2-methyl-anilino)-5-benzylthio-1,2,4-triazole

15 Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) the title compound was prepared as a white solid. MS (ESI) 297.2 (M+H)<sup>+</sup>.

#### Example 63

20 Preparation of 3-(2-methyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1 (d), the  
25 title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

#### Example 64

Preparation of 3-(2-methyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and  
30 bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

#### Example 65

35 Preparation of 3-(2-methyl-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d) except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-



(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 298.2 (M+H)<sup>+</sup>.

#### Example 66

5 Preparation of 3-(2-methyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 275.2 (M+H)<sup>+</sup>.

10

#### Example 67

Preparation of 3-(2-methyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 315.2 (M+H)<sup>+</sup>.

15

#### Example 68

20 Preparation of 3-(2-methyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 302.0 (M+H)<sup>+</sup>.

25

#### Example 69

Preparation of 3-(2-methyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 311.2 (M+H)<sup>+</sup>.

30

#### Example 70

35 Preparation of 3-(2-methyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-

difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 333.2 (M+H)<sup>+</sup>.

#### Example 71

5 Preparation of 3-(2-methyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 327.2 (M+H)<sup>+</sup>.

10

#### Example 72

Preparation of 3-(2-methyl-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-chloromethyl-2-methylthiazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 318.2 (M+H)<sup>+</sup>.

15

#### Example 73

20 Preparation of 3-(2-methyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 298.2 (M+H)<sup>+</sup>.

25

#### Example 74

Preparation of 3-(2-methyl-anilino)-5-(furan-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-furan (Berry, J. M.; Watson, C. Y.; Whish, W. J. D.; Threadgill, M. D. *J. Chem. Soc. Perkin Trans. 1* **1997**, 8, 1147) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 287.2 (M+H)<sup>+</sup>.

35

Example 75Preparation of 3-(2-methyl-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-methyl-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* **1988**, 29(1), 117) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 317.2 (M+H)<sup>+</sup>.

10

Example 76Preparation of 3-(2-methyl-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-chloro-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* **1988**, 29(1), 117) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 337.2 (M+H)<sup>+</sup>.

20

Example 77Preparation of 3-(2-methyl-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-methyl-thiophene (Moradpour, A. J. *Chem. Soc. Perkin Trans. 1*, **1993**, 1, 7) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 317.2 (M+H)<sup>+</sup>.

30

Example 78Preparation of 3-(2-methyl-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-chloro-thiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 337.2 (M+H)<sup>+</sup>.

35

### Example 79

#### Preparation of 5-(5-*o*-tolyl amino-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carboxylic acid ethyl ester

5        Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 5-chloromethyl-furan-2-carboxylic acid ethyl ester was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 359.2 (M+H)<sup>+</sup>.

10

### Example 80

#### Preparation of 3-(2-methyl-anilino)-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole

15        Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-bromo-thiophene (Clapp, R. C.; Clark, J. H; Vaughan, J. R.; English, J. P.; Anderson, G. W. *J. Am. Chem. Soc.* **1947**, *60*, 1549) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid . MS (ESI) 381.0 (M)<sup>+</sup>.

20

### Example 81

#### Preparation of 5-(5-*o*-tolyl amino-4*H*-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carbaldehyde

25        Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 5-chloromethyl-furan-2-carbaldehyde (Sanda, K.; Rigal, L.; Delmas, M.; Gaset, A. *Synthesis* **1992**, *6*, 541) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 315.2 (M+H)<sup>+</sup>.

30

### Example 82

#### Preparation of 3-(2-methyl-anilino)-5-(thiophen-3-ylthio)-1,2,4-triazole

35        Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-chloromethyl-thiophene (Lamy, J.; Lavit, D.; Buu-Hoi, N. P. *J. Chem. Soc.* **1958**, 4202) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

Example 83Preparation of 3-(2-methyl-anilino)-5-(furan-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *o*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-chloromethyl-furan (Arena, G.; Cali, R.; Maccarone, E.; Passerini, A. *J. Chem. Soc. Perkin Trans. 2* **1993**, *10*, 1941) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 287.2 (M+H)<sup>+</sup>.

Example 84Preparation of 3-(4-chloro-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a), the title compound was prepared as a white solid. MS (ESI) 317.2 (M+H)<sup>+</sup>.

Example 85Preparation of 3-(4-chloro-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 322.7 (M)<sup>+</sup>.

Example 86Preparation of 3-(4-chloro-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 323.2 (M+H)<sup>+</sup>.

Example 87Preparation of 3-(4-chloro-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 318.2 (M+H)<sup>+</sup>.

Example 88

Preparation of 3-(4-chloro-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 295.2 (M+H)<sup>+</sup>.

Example 89

Preparation of 3-(4-chloro-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 335.2 (M+H)<sup>+</sup>.

Example 90

Preparation of 3-(4-chloro-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 322.0 (M+H)<sup>+</sup>.

Example 91

Preparation of 3-(4-chloro-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 331.0 (M+H)<sup>+</sup>.

Example 92

Preparation of 3-(4-chloro-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 352.8 (M)<sup>+</sup>.

Example 93Preparation of 3-(4-chloro-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 347.0 (M+H)<sup>+</sup>.

Example 94Preparation of 3-(4-chloro-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-chloromethyl-2-methylthiazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 338.2 (M+H)<sup>+</sup>.

Example 95Preparation of 3-(4-chloro-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-chlorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 318.0 (M+H)<sup>+</sup>.

Example 96Preparation of 3-(4-methoxy-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a), the title compound was prepared as a white solid. MS (ESI) 313.2 (M+H)<sup>+</sup>.

Example 97Preparation of 3-(4-methoxy-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 319.0 (M+H)<sup>+</sup>.

Example 98Preparation of 3-(4-methoxy-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 319.2 (M+H)<sup>+</sup>.

Example 99Preparation of 3-(4-methoxy-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 314.2 (M+H)<sup>+</sup>.

Example 100Preparation of 3-(4-methoxy-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 291.2 (M+H)<sup>+</sup>.

Example 101Preparation of 3-(4-methoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 331.2 (M+H)<sup>+</sup>.

Example 102Preparation of 3-(4-methoxy-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole



Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 318.2 (M+H)<sup>+</sup>.

#### Example 103

##### Preparation of 3-(4-methoxy-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 327.2 (M+H)<sup>+</sup>.

#### Example 104

##### Preparation of 3-(4-methoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 349.0 (M+H)<sup>+</sup>.

#### Example 105

##### Preparation of 3-(4-methoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 343.0 (M+H)<sup>+</sup>.

#### Example 106

##### Preparation of 3-(4-methoxy-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-chloromethyl-2-methylthiazole was substituted for benzyl

bromide in step 1(d), the title compound was prepared as a white solid (2%).  
MS (ESI) 334.2 (M+H)<sup>+</sup>.

#### Example 107

##### Preparation of 3-(4-methoxy-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 314.2 (M+H)<sup>+</sup>.

#### Example 108

##### Preparation of 3-(4-methoxy-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-chloro-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* **1988**, 29(1), 117) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 353.2 (M+H)<sup>+</sup>.

#### Example 109

##### Preparation of 3-(4-methoxy-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *p*-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-chloro-thiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 353.0 (M+H)<sup>+</sup>.

#### Example 110

##### Preparation of 4-(5-benzylthio-1*H*-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a), the title compound was prepared as a white solid. MS (ESI) 341.0 (M+H)<sup>+</sup>.

Example 111Preparation of 4-(5-(cyclohexylmethylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

5           Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 347.2 (M+H)<sup>+</sup>.

10

Example 112Preparation of 4-(5-(pyridin-4-ylmethylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

15           Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 342.2 (M+H)<sup>+</sup>.

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Example 113Preparation of 4-(5-(2-methyl-2-butenylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

25           Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 319.0 (M+H)<sup>+</sup>.

Example 114

30   Preparation of 4-(5-(2-fluoro-benzylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

35           Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 359.2 (M+H)<sup>+</sup>.

Example 115Preparation of 4-(5-(5-methyl-isoxazol-3-ylmethylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

5        Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 346.0 (M+H)<sup>+</sup>.

Example 116Preparation of 4-(5-(2-methyl-benzylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

10        Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 355.0 (M+H)<sup>+</sup>.

Example 117Preparation of 4-(5-(3-methoxy-benzylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

20        Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 371.0 (M+H)<sup>+</sup>.

Example 118Preparation of 4-(5-(3,4-difluoro-benzylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

30        Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 377.0 (M+H)<sup>+</sup>.

Example 119Preparation of 4-(5-(2-methoxy-benzylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 371.0 (M+H)<sup>+</sup>.

Example 120Preparation of 4-(5-(2-methyl-thiazol-4-ylmethylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-chloromethyl-2-methylthiazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 362.0 (M+H)<sup>+</sup>.

Example 121Preparation of 4-(5-(pyridin-2-ylmethylthio)-1H-[1,2,4]triazol-3-ylamino)-benzoic acid methyl ester

Following the procedure of Example 1(a)-1(d), except *p*-methoxycarbonylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 342.2 (M+H)<sup>+</sup>.

Example 122Preparation of 3-(3,4-dimethoxy-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a), the title compound was prepared as a white solid. MS (ESI) 343.0 (M+H)<sup>+</sup>.

Example 123Preparation of 3-(3,4-dimethoxy-anilino)-5-(3-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 373.2 (M+H)<sup>+</sup>.

#### Example 124

##### Preparation of 3-(3,4-dimethoxy-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 349.2 (M+H)<sup>+</sup>.

#### Example 125

##### Preparation of 3-(3,4-dimethoxy-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 344.2 (M+H)<sup>+</sup>.

#### Example 126

##### Preparation of 3-(3,4-dimethoxy-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 321.2 (M+H)<sup>+</sup>.

#### Example 127

##### Preparation of 3-(3,4-dimethoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 361.2 (M+H)<sup>+</sup>.

#### Example 128

##### Preparation of 3-(3,4-dimethoxy-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 348.2 (M+H)<sup>+</sup>.

#### Example 129

##### Preparation of 3-(3,4-dimethoxy-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 357.2 (M+H)<sup>+</sup>.

#### Example 130

##### Preparation of 3-(3,4-dimethoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 379.0 (M+H)<sup>+</sup>.

#### Example 131

##### Preparation of 3-(3,4-dimethoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 373.0 (M+H)<sup>+</sup>.

#### Example 132

##### Preparation of 3-(3,4-dimethoxy-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-chloromethyl-2-methylthiazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 364.2 (M+H)<sup>+</sup>.

#### Example 133

##### Preparation of 3-(3,4-dimethoxy-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 344.0 (M+H)<sup>+</sup>.

#### Example 134

##### Preparation of 3-(3,4-dimethoxy-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 349.0 (M+H)<sup>+</sup>.

#### Example 135

##### Preparation of 3-(2-phenyl-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-phenyl-phenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) the title compound was prepared as a white solid. MS (ESI) 359.2 (M+H)<sup>+</sup>.



### Example 136

#### Preparation of 3-(2-phenyl-anilino)-5-(3-methoxybenzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-phenyl-phenyl  
5 isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-methoxyphenyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 389.0 (M+H)<sup>+</sup>.

### Example 137

#### Preparation of 3-(2-phenyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-phenyl-phenyl  
isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and  
bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the  
title compound was prepared as a white solid. MS (ESI) 365.2 (M+H)<sup>+</sup>.

15

### Example 138

#### Preparation of 3-(2-phenyl-anilino)-5-(pyridin-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d) except 2-phenyl-phenyl  
isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-  
20 (chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 360.2 (M+H)<sup>+</sup>.

### Example 139

#### Preparation of 3-(2-phenyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-phenyl-phenyl  
isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-  
bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the  
title compound was prepared as a white solid. MS (ESI) 337.2 (M+H)<sup>+</sup>.

25

### Example 140

#### Preparation of 3-(2-phenyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-phenyl-phenyl  
isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-  
fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title  
35 compound was prepared as a white solid. MS (ESI) 376.8 (M)<sup>+</sup>.

Example 141Preparation of 3-(2-phenyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-phenyl-phenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 364.0 (M+H)<sup>+</sup>.

Example 142Preparation of 3-(2-phenyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-phenyl-phenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 373.0 (M+H)<sup>+</sup>.

Example 143Preparation of 3-(2-phenyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-phenyl-phenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 395.0 (M+H)<sup>+</sup>.

Example 144Preparation of 3-(2-phenyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-phenyl-phenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 389.2 (M+H)<sup>+</sup>.

Example 145Preparation of 3-(2-phenyl-anilino)-5-(2-methyl-thiazol-4-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-phenyl-phenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-chloromethyl-2-methylthiazole was substituted for benzyl bromide in step

1(d), the title compound was prepared as a white solid. MS (ESI) 380.0 (M+H)<sup>+</sup>.

#### Example 146

5 Preparation of 3-(2-phenyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-phenyl-phenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 365.2 (M+H)<sup>+</sup>.

10

#### Example 147

Preparation of [5-(benzylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) the title compound was prepared as a white solid. MS (ESI) 284.2 (M+H)<sup>+</sup>.

15

#### Example 148

Preparation of [5-(3-methoxybenzylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-methoxyphenyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 314.2 (M+H)<sup>+</sup>.

20

#### Example 149

Preparation of [5-(cyclohexylmethylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 290.2 (M+H)<sup>+</sup>.

30

#### Example 150

Preparation of [5-(pyridin-4-ylmethylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

35

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-

(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 285.2 (M+H)<sup>+</sup>.

#### Example 151

5 Preparation of [5-(2-methyl-2-butenylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the  
10 title compound was prepared as a white solid. MS (ESI) 262.0 (M+H)<sup>+</sup>.

#### Example 152

Preparation of [5-(2-fluoro-benzylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

15 Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 302.2 (M+H)<sup>+</sup>.

#### Example 153

20 Preparation of [5-(5-methyl-isoxazol-3-yl)methylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step  
25 1(d), the title compound was prepared as a white solid. MS (ESI) 289.0 (M+H)<sup>+</sup>.

#### Example 154

30 Preparation of [5-(2-methyl-benzylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the  
35 title compound was prepared as a white solid. MS (ESI) 298.2 (M+H)<sup>+</sup>.

Example 155Preparation of [5-(3,4-difluoro-benzylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 320.2 (M+H)<sup>+</sup>.

Example 156

10 Preparation of [5-(2-methoxy-benzylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 314.2 (M+H)<sup>+</sup>.

Example 157

20 Preparation of [5-(pyridin-2-ylmethylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 285.2 (M+H)<sup>+</sup>.

Example 158

25 Preparation of [5-(2-methyl-thiazol-4-ylmethylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-chloromethyl-2-methylthiazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 305.2 (M+H)<sup>+</sup>.

Example 159

35 Preparation of [5-(thiophen-2-ylthio)-1H-[1,2,4]triazol-3-yl]-pyridin-3-yl-amine

Following the procedure of Example 1(a)-1(d), except 3-pyridyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 290.0 (M+H)<sup>+</sup>.

5

#### Example 160

##### Preparation of 3-(2-ethyl-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) the title compound was prepared as a white solid. MS (ESI) 311.4 (M+H)<sup>+</sup>.

10

#### Example 161

##### Preparation of 3-(2-ethyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1 (d), the title compound was prepared as a white solid. MS (ESI) 317.2 (M+H)<sup>+</sup>.

15

#### Example 162

##### Preparation of 3-(2-ethyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 329.2 (M+H)<sup>+</sup>.

20

25

#### Example 163

##### Preparation of 3-(2-ethyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 347.0 (M+H)<sup>+</sup>.

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#### Example 164

##### Preparation of 3-(2-ethyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-

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bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 289.0 (M+H)<sup>+</sup>.

#### Example 165

5 Preparation of 3-(2-ethyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 329.2 (M+H)<sup>+</sup>.

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#### Example 166

Preparation of 3-(2-ethyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 325.2 (M+H)<sup>+</sup>.

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#### Example 167

20 Preparation of 3-(2-ethyl-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chlorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 345.0 (M+H)<sup>+</sup>.

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#### Example 168

Preparation of 3-(2-ethyl-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 341.2 (M+H)<sup>+</sup>.

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#### Example 169

35 Preparation of 3-(2-ethyl-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-

methylenedioxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 355.0 (M+H)<sup>+</sup>.

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#### Example 170

##### Preparation of 3-(2-ethyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 316.0 (M+H)<sup>+</sup>.

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#### Example 171

##### Preparation of 3-(2-ethyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 312.2 (M+H)<sup>+</sup>.

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#### Example 172

##### Preparation of 3-(2-ethyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-ethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 341.2 (M+H)<sup>+</sup>.

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#### Example 173

##### Preparation of 3-(2-methoxy-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) the title compound was prepared as a white solid. MS (ESI) 313.2 (M+H)<sup>+</sup>.

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#### Example 174

##### Preparation of 3-(2-methoxy-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole



Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 319.0 (M+H)<sup>+</sup>.

#### Example 175

##### Preparation of 3-(2-methoxy-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 331.2 (M+H)<sup>+</sup>.

#### Example 176

##### Preparation of 3-(2-methoxy-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 319.2 (M+H)<sup>+</sup>.

#### Example 177

##### Preparation of 3-(2-methoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 349.0 (M+H)<sup>+</sup>.

#### Example 178

##### Preparation of 3-(2-methoxy-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide

in step 1(d), the title compound was prepared as a white solid. MS (ESI) 291.2 (M+H)<sup>+</sup>.

#### Example 179

5 Preparation of 3-(2-methoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 331.2 (M+H)<sup>+</sup>.

#### Example 180

15 Preparation of 3-(2-methoxy-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 327.2 (M+H)<sup>+</sup>.

#### Example 181

20 Preparation of 3-(2-methoxy-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chlorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 347.0 (M+H)<sup>+</sup>.

#### Example 182

30 Preparation of 3-(2-methoxy-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 343.0 (M+H)<sup>+</sup>.

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Example 183Preparation of 3-(2-methoxy-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-methylenedioxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 357.0 (M+H)<sup>+</sup>.

Example 184Preparation of 3-(2-methoxy-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 316.0 (M+H)<sup>+</sup>.

Example 185Preparation of 3-(2-methoxy-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 314.2 (M+H)<sup>+</sup>.

Example 186Preparation of 3-(2-methoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid (49%). MS (ESI) 343.0 (M+H)<sup>+</sup>.

Example 187Preparation of 3-(2-methoxy-anilino)-5-(furan-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-furan (Berry, J. M.; Watson, C. Y.; Whish, W. J. D.; Threadgill, M. D. *J. Chem. Soc. Perkin Trans. 1* **1997**, 8, 1147) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

#### Example 188

##### Preparation of 3-(2-methoxy-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-methyl-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* **1988**, 29(1), 117) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 333.2 (M+H)<sup>+</sup>.

#### Example 189

##### Preparation of 3-(2-methoxy-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-chloro-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* **1988**, 29(1), 117) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 353.2 (M+H)<sup>+</sup>.

#### Example 190

##### Preparation of 3-(2-methoxy-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-methyl-thiophene (Moradpour, A. *J. Chem. Soc. Perkin Trans. 1*, **1993**, 1, 7) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 333.2 (M+H)<sup>+</sup>.

Example 191Preparation of 3-(2-methoxy-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-chloro-thiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 353.0 (M+H)<sup>+</sup>.

Example 192Preparation of 5-(5-(2-methoxyphenylamino)-4H-[1,2,4]triazol-3-yl)sulfanylmethyl)-furan-2-carboxylic acid ethyl ester

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 5-chloromethyl-furan-2-carboxylic acid ethyl ester was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 375.0 (M+H)<sup>+</sup>.

Example 193Preparation of 3-(2-methoxy-anilino)-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-bromo-thiophene (Clapp, R. C.; Clark, J. H.; Vaughan, J. R.; English, J. P.; Anderson, G. W. *J. Am. Chem. Soc.* **1947**, 60, 1549) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 396.8 (M-H)<sup>+</sup>.

Example 194Preparation of 3-(2-methoxy-anilino)-5-(thiophen-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-chloromethyl-thiophene (Lamy, J.; Lavit, D.; Buu-Hoi, N. P. *J. Chem. Soc.* **1958**, 4202) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 319.0 (M+H)<sup>+</sup>.

Example 195Preparation of 3-(2-methoxy-anilino)-5-(furan-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in  
5 step 1(a) and 3-chloromethyl-furan (Arena, G.; Cali, R.; Maccarone, E.; Passerini, A. *J. Chem. Soc. Perkin Trans. 2* **1993**, 10, 1941) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

Example 196Preparation of 3-(2-isopropyl-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in  
10 step 1(a) the title compound was prepared as a white solid. MS (ESI) 325.2 (M+H)<sup>+</sup>.

Example 197Preparation of 3-(2-isopropyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in  
20 step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 331.2 (M+H)<sup>+</sup>.

Example 198Preparation of 3-(2-isopropyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in  
25 step 1(a) and 4-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 343.0 (M+H)<sup>+</sup>.

Example 199Preparation of 3-(2-isopropyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in  
35 step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in

step 1(d), the title compound was prepared as a white solid. MS (ESI) 331.2 (M+H)<sup>+</sup>.

#### Example 200

5 Preparation of 3-(2-isopropyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 361.2 (M+H)<sup>+</sup>.

#### Example 201

15 Preparation of 3-(2-isopropyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

#### Example 202

Preparation of 3-(2-isopropyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 343.0 (M+H)<sup>+</sup>.

#### Example 203

30 Preparation of 3-(2-isopropyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 339.2 (M+H)<sup>+</sup>.

Example 204Preparation of 3-(2-isopropyl-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chlorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 359.2 (M+H)<sup>+</sup>.

Example 205Preparation of 3-(2-isopropyl-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 355.2 (M+H)<sup>+</sup>.

Example 206Preparation of 3-(2-isopropyl-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-methylenedioxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 369.2 (M+H)<sup>+</sup>.

Example 207Preparation of 3-(2-isopropyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylisothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 330.2 (M+H)<sup>+</sup>.



Example 208Preparation of 3-(2-isopropyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 326.2 (M+H)<sup>+</sup>.

Example 209Preparation of 3-(2-isopropyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 355.2 (M+H)<sup>+</sup>.

Example 210Preparation of 3-(2-isopropyl-anilino)-5-(furan-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-furan (Berry, J. M.; Watson, C. Y.; Whish, W. J. D.; Threadgill, M. D. *J. Chem. Soc. Perkin Trans. 1* **1997**, 8, 1147) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 315.2 (M+H)<sup>+</sup>.

Example 211Preparation of 3-(2-isopropyl-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-methyl-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* **1988**, 29(1), 117) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 345.2 (M+H)<sup>+</sup>.

Example 212

Preparation of 3-(2-isopropyl-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in  
5 step 1(a) and 2-chloromethyl-3-chloro-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* **1988**, 29(1), 117) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 365.2 (M+H)<sup>+</sup>.

Example 213

Preparation of 3-(2-isopropyl-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in  
15 step 1(a) and 2-chloromethyl-5-methyl-thiophene (Moradpour, A. *J. Chem. Soc. Perkin Trans. 1*, **1993**, 1, 7) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 345.2 (M+H)<sup>+</sup>.

Example 214

Preparation of 3-(2-isopropyl-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in  
25 step 1(a) and 2-chloromethyl-5-chloro-thiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 365.2 (M+H)<sup>+</sup>.

Example 215

Preparation of 5-(5-(2-isopropylphenylamino)-4H-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carboxylic acid ethyl ester

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in  
step 1(a) and 5-chloromethyl-furan-2-carboxylic acid ethyl ester was  
35 substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 387.2 (M+H)<sup>+</sup>.

### Example 216

#### Preparation of 5-(5-(2-isopropyl amino)-4H-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carbaldehyde

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 5-chloromethyl-furan-2-carbaldehyde (Sanda, K.; Rigal, L.; Delmas, M.; Gaset, A. *Synthesis* **1992**, 6, 541) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 343.0 (M+H)<sup>+</sup>.

### Example 217

#### Preparation of 3-(2-isopropyl-anilino)-5-(thiophen-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-chloromethyl-thiophene (Lamy, J.; Lavit, D.; Buu-Hoi, N. P. *J. Chem. Soc.* **1958**, 4202) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 331.2 (M+H)<sup>+</sup>.

### Example 218

#### Preparation of 3-(2-isopropyl-anilino)-5-(furan-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-isopropylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-chloromethyl-furan (Arena, G.; Cali, R.; Maccarone, E.; Passerini, A. *J. Chem. Soc. Perkin Trans. 2* **1993**, 10, 1941) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 315.2 (M+H)<sup>+</sup>.

### Example 219

#### Preparation of 3-(3-methyl-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a), the title compound was prepared as a white solid. MS (ESI) 297.2 (M+H)<sup>+</sup>.

### Example 220

#### Preparation of 3-(3-methyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-

chloromethylthiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

#### Example 221

##### Preparation of 3-(3-methyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

#### Example 222

##### Preparation of 3-(3-methyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 315.2 (M+H)<sup>+</sup>.

#### Example 223

##### Preparation of 3-(3-methyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 275.2 (M+H)<sup>+</sup>.

#### Example 224

##### Preparation of 3-(3-methyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 315.2 (M+H)<sup>+</sup>.

#### Example 225

##### Preparation of 3-(3-methyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step

1(d), the title compound was prepared as a white solid. MS (ESI) 302.2 (M+H)<sup>+</sup>.

#### Example 226

5 Preparation of 3-(3-methyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 311.4 (M+H)<sup>+</sup>.

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#### Example 227

Preparation of 3-(3-methyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 333.2 (M+H)<sup>+</sup>.

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#### Example 228

Preparation of 3-(3-methyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 327.2 (M+H)<sup>+</sup>.

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#### Example 229

Preparation of 3-(3-methyl-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chlorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 331.2 (M+H)<sup>+</sup>.

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#### Example 230

Preparation of 3-(3-methyl-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 327.2 (M+H)<sup>+</sup>.

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Example 231Preparation of 3-(3-methyl-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole

5        Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-methylenedioxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 341.2 (M+H)<sup>+</sup>.

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Example 232Preparation of 3-(3-methyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

15        Following the procedure of Example 1(a)-1(d), except *m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 298.2 (M+H)<sup>+</sup>.

Example 233Preparation of 3-(3-methyl-anilino)-5-(furan-2-ylthio)-1,2,4-triazole

20        Following the procedure of Example 1(a)-1(d), except 3-*m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-furan (Berry, J. M.; Watson, C. Y.; Whish, W. J. D.; Threadgill, M. D. *J. Chem. Soc. Perkin Trans. 1* 1997, 8, 1147) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS  
25        (ESI) 287.2 (M+H)<sup>+</sup>.

Example 234Preparation of 3-(3-methyl-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole

30        Following the procedure of Example 1(a)-1(d), except 3-*m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-methyl-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* 1988, 29(1), 117) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS  
35        (ESI) 317.2 (M+H)<sup>+</sup>.

Example 235Preparation of 3-(3-methyl-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3-*m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-chloro-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* **1988**, 29(1), 117) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 337.2 (M+H)<sup>+</sup>.

Example 236Preparation of 3-(3-methyl-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3-*m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-methyl-thiophene (Moradpour, A. *J. Chem. Soc. Perkin Trans. I*, **1993**, 1, 7) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 317.2 (M+H)<sup>+</sup>.

Example 237Preparation of 3-(3-methyl-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3-*m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-chloro-thiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 337.2 (M+H)<sup>+</sup>.

Example 238Preparation of 5-(5-(3-methylphenylamino)-4H-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carboxylic acid ethyl ester

Following the procedure of Example 1(a)-1(d), except 3-*m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 5-chloromethyl-furan-2-carboxylic acid ethyl ester was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 359.2 (M+H)<sup>+</sup>.

Example 239Preparation of 3-(3-methyl-anilino)-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3-*m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-bromo-thiophene (Clapp, R. C.; Clark, J. H.; Vaughan, J. R.; English, J. P.; Anderson, G. W. *J. Am. Chem. Soc.* **1947**, *60*, 1549) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 381.0 (M+H)<sup>+</sup>.

Example 240Preparation of 5-(5-(3-methylphenylamino)-4H-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carbaldehyde

Following the procedure of Example 1(a)-1(d), except 3-*m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 5-chloromethyl-furan-2-carbaldehyde (Sanda, K.; Rigal, L.; Delmas, M.; Gaset, A. *Synthesis* **1992**, *6*, 541) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 315.2 (M+H)<sup>+</sup>.

Example 241Preparation of 3-(3-methyl-anilino)-5-(thiophen-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3-*m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-chloromethyl-thiophene (Lamy, J.; Lavit, D.; Buu-Hoi, N. P. *J. Chem. Soc.* **1958**, 4202) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 303.2 (M+H)<sup>+</sup>.

Example 242Preparation of 3-(3-methyl-anilino)-5-(furan-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 3-*m*-tolyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-chloromethyl-furan (Arena, G.; Cali, R.; Maccarone, E.; Passerini, A. *J. Chem. Soc. Perkin Trans. 2* **1993**, *10*, 1941) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 287.2 (M+H)<sup>+</sup>.



Example 243Preparation of 3-(4-*n*-butyl-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) the title compound was prepared as a white solid. MS (ESI) 339.2 (M+H)<sup>+</sup>.

Example 244Preparation of 3-(4-*n*-butyl-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 345.2 (M+H)<sup>+</sup>.

Example 245Preparation of 3-(4-*n*-butyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 357.2 (M+H)<sup>+</sup>.

Example 246Preparation of 3-(4-*n*-butyl-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 375.2 (M+H)<sup>+</sup>.

Example 247Preparation of 3-(4-*n*-butyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 317.2 (M+H)<sup>+</sup>.

Example 248Preparation of 3-(4-*n*-butyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 357.2 (M+H)<sup>+</sup>.

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#### Example 249

##### Preparation of 3-(4-*n*-butyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 353.2 (M+H)<sup>+</sup>.

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#### Example 250

##### Preparation of 3-(4-*n*-butyl-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chlorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 373.2 (M+H)<sup>+</sup>.

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#### Example 251

##### Preparation of 3-(4-*n*-butyl-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 369.2 (M+H)<sup>+</sup>.

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#### Example 252

##### Preparation of 3-(4-*n*-butyl-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-methylenedioxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 383.2 (M+H)<sup>+</sup>.

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Example 253Preparation of 3-(4-*n*-butyl-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 344.2 (M+H)<sup>+</sup>.

Example 254Preparation of 3-(4-*n*-butyl-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 340.2 (M+H)<sup>+</sup>.

Example 255Preparation of 3-(4-*n*-butyl-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-*n*-butylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 369.2 (M+H)<sup>+</sup>.

Example 256Preparation of 3-(2,4-dimethoxy-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) the title compound was prepared as a white solid. MS (ESI) 343.0 (M+H)<sup>+</sup>.

Example 257Preparation of 3-(2,4-dimethoxy-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1 (d), the title compound was prepared as a white solid. MS (ESI) 349.0 (M+H)<sup>+</sup>.

Example 258Preparation of 3-(2,4-dimethoxy-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole

5        Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 361.0 (M+H)<sup>+</sup>.

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Example 259Preparation of 3-(2,4-dimethoxy-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

15        Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 349.0 (M+H)<sup>+</sup>.

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Example 260Preparation of 3-(2,4-dimethoxy-anilino)- (3,4-difluoro-benzylthio)-1,2,4-triazole

25        Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 379.0 (M+H)<sup>+</sup>.

Example 261

30        Preparation of 3-(2,4-dimethoxy-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

35        Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 321.2 (M+H)<sup>+</sup>.

Example 262Preparation of 3-(2,4-dimethoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 361.0 (M+H)<sup>+</sup>.

Example 263Preparation of 3-(2,4-dimethoxy-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 357.2 (M+H)<sup>+</sup>.

Example 264Preparation of 3-(2,4-dimethoxy-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chlorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 377.0 (M+H)<sup>+</sup>.

Example 265Preparation of 3-(2,4-dimethoxy-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 373.2 (M+H)<sup>+</sup>.

Example 266Preparation of 3-(2,4-dimethoxy-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-methylenedioxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 387.2 (M+H)<sup>+</sup>.

Example 267Preparation of 3-(2,4-dimethoxy-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 348.0 (M+H)<sup>+</sup>.

Example 268Preparation of 3-(2,4-dimethoxy-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 344.2 (M+H)<sup>+</sup>.

Example 269Preparation of 3-(2,4-dimethoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,4-dimethoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 373.2 (M+H)<sup>+</sup>.

Example 270Preparation of 3-(2-methyl-4-methoxy-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) the title compound was prepared as a white solid. MS (ESI) 327.2 (M+H)<sup>+</sup>.

Example 271Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethylthiophene was substituted for benzyl bromide in step 1 (d), the title compound was prepared as a white solid. MS (ESI) 333.2 (M+H)<sup>+</sup>.

Example 272Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 345.0 (M+H)<sup>+</sup>.

Example 273Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 333.2 (M+H)<sup>+</sup>.

Example 274Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 363.0 (M+H)<sup>+</sup>.

#### Example 275

##### Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 305.2 (M+H)<sup>+</sup>.

#### Example 276

##### Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 345.0 (M+H)<sup>+</sup>.

#### Example 277

##### Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 341.2 (M+H)<sup>+</sup>.

#### Example 278

##### Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole



Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chlorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 361.0 (M+H)<sup>+</sup>.

#### Example 279

##### Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(4-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 357.2 (M+H)<sup>+</sup>.

#### Example 280

##### Preparation 3-(2-methyl-4-methoxy-anilino)-5-(3,4-methylenedioxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-methylenedioxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 371.0 (M+H)<sup>+</sup>.

#### Example 281

##### Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(5-methyl-isoxazol-3-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-(chloromethyl)-5-methylisoxazole was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 332.2 (M+H)<sup>+</sup>.

#### Example 282

##### Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(pyridin-2-ylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-(chloromethyl)pyridine was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 328.2 (M+H)<sup>+</sup>.

#### Example 283

##### Preparation of 3-(2-methyl-4-methoxy-anilino)-5-(2-methoxy-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2-methyl-4-methoxyphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methoxybenzyl chloride was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 357.2 (M+H)<sup>+</sup>.

#### Example 284

##### Preparation of 3-(2,6-dimethyl-anilino)-5-benzylthio-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,6-dimethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) the title compound was prepared as a white solid. MS (ESI) 311.4 (M+H)<sup>+</sup>.

#### Example 285

##### Preparation of 3-(2,6-dimethyl-anilino)-5-(4-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,6-dimethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 4-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 329.2 (M+H)<sup>+</sup>.

#### Example 286

##### Preparation of 3-(2,6-dimethyl-anilino)-5-(cyclohexylmethylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,6-dimethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and bromomethylcyclohexane was substituted for benzyl bromide in

step 1(d), the title compound was prepared as a white solid . MS (ESI) 317.2 (M+H)<sup>+</sup>.

#### Example 287

5 Preparation of 3-(2,6-dimethyl-anilino)- (3,4-difluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,6-dimethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3,4-difluorobenzyl bromide was substituted for benzyl bromide  
10 in step 1(d), the title compound was prepared as a white solid. MS (ESI) 347.0 (M+H)<sup>+</sup>.

#### Example 288

15 Preparation of 3-(2,6-dimethyl-anilino)-5-(2-methyl-2-butenylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,6-dimethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 1-bromo-3-methylbut-2-ene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI)  
20 289.0 (M+H)<sup>+</sup>.

#### Example 289

Preparation of 3-(2,6-dimethyl-anilino)-5-(2-fluoro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,6-dimethylphenyl isothiocyanate was substituted for phenylisothiocyanate in  
25 step 1(a) and 2-fluorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 329.2 (M+H)<sup>+</sup>.

#### Example 290

30 Preparation of 3-(2,6-dimethyl-anilino)-5-(2-methyl-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,6-dimethylphenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-methylbenzyl bromide was substituted for benzyl bromide in  
35 step 1(d), the title compound was prepared as a white solid. MS (ESI) 325.2 (M+H)<sup>+</sup>.

Example 291Preparation of 3-(2,6-dimethyl-anilino)-5-(2-chloro-benzylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 2,6-dimethylphenyl isothiocyanate was substituted for phenylisothiocyanate in  
5 step 1(a) and 2-chlorobenzyl bromide was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 345.0 (M+H)<sup>+</sup>.

Example 29210 Preparation of 3-(4-fluoro-anilino)-5-(furan-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-fluorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-furan (Berry, J. M.; Watson, C. Y.; Whish, W. J. D.; Threadgill, M. D. *J. Chem. Soc. Perkin Trans. 1* 1997, 8, 1147) was substituted for benzyl  
15 bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 291.2 (M+H)<sup>+</sup>.

Example 29320 Preparation of 3-(4-fluoro-anilino)-5-(3-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-fluorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-methyl-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* 1988, 29(1), 117) was substituted for benzyl  
25 bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 321.0 (M+H)<sup>+</sup>.

Example 29430 Preparation of 3-(4-fluoro-anilino)-5-(3-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-fluorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-3-chloro-thiophene (Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.* 1988, 29(1), 117) was substituted for benzyl  
35 bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 341.2 (M+H)<sup>+</sup>.

Example 295Preparation of 3-(4-fluoro-anilino)-5-(5-methyl-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-fluorophenyl  
5 isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-methyl-thiophene (Moradpour, A. *J. Chem. Soc. Perkin Trans. 1*, 1993, 1, 7) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 321.0 (M+H)<sup>+</sup>.

Example 296Preparation of 3-(4-fluoro-anilino)-5-(5-chloro-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-fluorophenyl  
15 isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-chloro-thiophene was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 341.2 (M+H)<sup>+</sup>.

Example 297Preparation of 5-(5-(4-fluorophenylamino)-4H-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carboxylic acid ethyl ester

Following the procedure of Example 1(a)-1(d), except 4-fluorophenyl  
isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 5-chloromethyl-furan-2-carboxylic acid ethyl ester was substituted for benzyl  
25 bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 363.2 (M+H)<sup>+</sup>.

Example 298Preparation of 3-(4-fluoro-anilino)-5-(5-bromo-thiophen-2-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-fluorophenyl  
isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 2-chloromethyl-5-bromo-thiophene (Clapp, R. C.; Clark, J. H.; Vaughan, J. R.; English, J. P.; Anderson, G. W. *J. Am. Chem. Soc.* 1947, 60, 1549) was  
35 substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 385.0 (M)<sup>+</sup>.

Example 299Preparation of 5-(5-(4-fluorophenylamino)-4H-[1,2,4]triazol-3-ylsulfanylmethyl)-furan-2-carbaldehyde

Following the procedure of Example 1(a)-1(d), except 4-fluorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 5-chloromethyl-furan-2-carbaldehyde (Sanda, K.; Rigal, L.; Delmas, M.; Gaset, A. *Synthesis* **1992**, 6, 541) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 319.0 (M+H)<sup>+</sup>.

Example 300Preparation of 3-(4-fluoro-anilino)-5-(thiophen-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-fluorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-chloromethyl-thiophene (Lamy, J.; Lavit, D.; Buu-Hoi, N. P. *J. Chem. Soc.* **1958**, 4202) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 307.2 (M+H)<sup>+</sup>.

Example 301Preparation of 3-(4-fluoro-anilino)-5-(furan-3-ylthio)-1,2,4-triazole

Following the procedure of Example 1(a)-1(d), except 4-fluorophenyl isothiocyanate was substituted for phenylisothiocyanate in step 1(a) and 3-chloromethyl-furan (Arena, G.; Cali, R.; Maccarone, E.; Passerini, A. *J. Chem. Soc. Perkin Trans. 2* **1993**, 10, 1941) was substituted for benzyl bromide in step 1(d), the title compound was prepared as a white solid. MS (ESI) 291.2 (M+H)<sup>+</sup>.

Example 302Preparation of 3-methyl-3-anilino-5-benzylthio-1,2,4-triazolea) 3-anilino-5-benzylthio-1 or/2-methyl ethyl ether-1,2,4-triazole

To a stirring solution of 3-anilino-5-benzylthio-1,2,4-triazole (0.68 g, 2.41 mmol) in 8 mL DMF was added NaH (0.125 g, 3.13 mmol). To this mixture was added chloromethyl ethyl ether (0.251 g, 2.65 mmol), and the solution was stirred overnight. The reaction mixture was poured into 50 ml H<sub>2</sub>O and extracted three times with EtOAc. The EtOAc extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated down. The crude mixture was subjected to column chromatography (silica gel, EtOAc/hexane) to provide the title compounds as a mixture of regioisomers as a light yellow oil (0.58 g,

71%). <sup>1</sup>H-NMR (400MHz, d6-DMSO) compound 1: δ9.33 (broad singlet, 1H), 7.51 (d, 2H, J=8.3 Hz), 7.42-7.22 (m, 8H), 5.23 (s, 2H), 4.47 (s, 2H), 3.43 (q, 2H, J=7.2 Hz), 1.04 (t, 3H, J=7.0 Hz). Compound 2: δ9.20 (broad singlet, 1H), 7.63 (d, 2H, J=7.6 Hz), 7.42-6.93 (m, 8H), 5.44 (s, 2H), 4.30 (s, 2H), 3.51 (q, 2H, J=7.1 Hz), 1.07 (t, 3H, J=7.0). MS (ESI) 341 (M+H)<sup>+</sup>.

b) 3-methyl-3-anilino-5-benzylthio-1,2,4-triazole

To a stirring solution of 3-anilino-5-benzylthio-1 or/2-methyl ethyl ether-1,2,4-triazole (50 mg, 0.15 mmol) in 1 ml THF was added NaH (11.8 mg, 0.30 mmol), and to this solution was added CH<sub>3</sub>I (0.036 ml, 0.57 mmol). The reaction mixture was stirred overnight. THF was removed and 0.5 ml TFA was added to the residue and stirred overnight. TFA was removed under vacuum and the mixture was purified by preparative HPLC to afford the title compound as a clear oil (28 mg, 53%). <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ3.3-7.25 (m, 10H), 4.27 (s, 2H), 3.40 (s, 3H). MS (ESI) 297 (M+H)<sup>+</sup>.

Example 303

Preparation of 3-ethyl-3-anilino-5-benzylthio-1,2,4-triazole

Following the procedure of Example 302(a)-(b) except iodoethane was used in step 302(b) instead of iodomethane, the title compound was isolated as a white solid. <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ7.42-7.26 (m, 10H), 4.26 (s, 2H), 3.86 (m, 2H), 1.20 (m, 3H). MS (ESI) 311 (M+H)<sup>+</sup>.

Example 304

Preparation of 3-n-propyl-3-anilino-5-benzylthio-1,2,4-triazole

Following the procedure of Example 302(a)-(b) except 1-iodopropane was used in step 302(b) instead of iodomethane, the title compound was isolated as a white solid (35%). <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ7.42-7.26 (m, 10H), 4.25 (s, 2H), 3.76 (t, 2H, J=6.5 Hz), 3.31 (t, 2H, J=1.4 Hz), 1.63 (m, 2H), 0.93 (t, 3H, J=7.4 Hz). MS (ESI) 325 (M+H)<sup>+</sup>.

Example 305

Preparation of 3-n-butyl-3-anilino-5-benzylthio-1,2,4-triazole

Following the procedure of Example 302(a)-(b) except 1-iodobutane was used in step 302(b) instead of iodomethane, the title compound was isolated as a white solid (31%). <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ7.42-7.22 (m, 10H), 4.26 (s, 2H), 3.80 (t, 2H, J=7.5 Hz), 3.31 (t, 2H, J=1.4 Hz), 1.59 (m, 2H), 1.36 (m, 2H), 0.92 (t, 3H, J=7.3 Hz). MS (ESI) 338 (M+H)<sup>+</sup>.

### Example 306

#### Preparation of 3-isopropyl-3-anilino-5-benzylthio-1,2,4-triazole

Following the procedure of Example 302(a)-(b) except 1-iodo-2-methyl propane was used in step 302(b) instead of iodomethane, the title compound was isolated as a white solid. <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ7.42-7.22 (m, 10H), 4.25 (s, 2H), 3.66 (d, 2H, J=7.6 Hz), 1.92 (m, 1H), 0.93 (d, 6H, J=6.7 Hz). MS (ESI) 338 (M+H)<sup>+</sup>.

### Example 307

#### Preparation of 3-allyl-3-anilino-5-benzylthio-1,2,4-triazole

Following the procedure of Example 302(a)-(b) except allyl bromide was used in step 302(b) instead of iodomethane, the title compound was isolated as a white solid (41%). <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ7.37-7.28 (m, 10H), 5.96 (m, 1H), 5.18 (m, 2H), 4.45 (s, 2H), 4.26 (s, 2H). MS (ESI) 323 (M+H)<sup>+</sup>.

### Example 308

#### Preparation of 3-benzyl-3-anilino-5-benzylthio-1,2,4-triazole

Following the procedure of Example 302(a)-(b) except benzyl bromide was used in step 302(b) instead of iodomethane, the title compound was isolated as a white solid (48%). <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ7.28-7.23 (m, 15H), 5.09 (s, 2H), 4.26 (s, 2H). MS (ESI) 373 (M+H)<sup>+</sup>.

### Example 309

#### Preparation of 3-methylacetate-3-anilino-5-benzylthio-1,2,4-triazole

Following the procedure of Example 302(a)-(b) except methyl bromoacetate was used in step 302(b) instead of iodomethane, the title compound was isolated as a white solid. <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ7.37-7.22 (m, 10H), 4.59 (s, 2H), 4.26 (s, 2H), 3.74 (s, 3H). MS (ESI) 355 (M+H)<sup>+</sup>.

### Example 310

#### Preparation of 3-methylacetate-3-(p-methyl)-anilino-5-benzylthio-1,2,4-triazole

Following the procedure of Example 302(a)-(b) except 3-(p-methyl)-anilino-5-benzylthio-1,2,4-triazole was used in step 302(a) instead of 3-



anilino-5-benzylthio-1,2,4-triazole and methyl bromoacetate was used in step 302(b) instead of iodomethane, the title compound was isolated as a clear oil. <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ7.38-7.09 (m, 9H), 4.56 (s, 2H), 4.27 (s, 2H), 3.75 (s, 3H), 2.37 (s, 3H). MS (ESI) 369 (M+H)<sup>+</sup>.

5

#### Example 311

##### Preparation of 3-methylacetate-3-(p-methoxy)-anilino-5-benzylthio-1,2,4-triazole

Following the procedure of Example 302(a)-(b) except 3-(p-methoxy)-anilino-5-benzylthio-1,2,4-triazole was used in step 302(a) instead of 3-anilino-5-benzylthio-1,2,4-triazole and methyl bromoacetate was used in step 302(b) instead of iodomethane, the title compound was isolated as a brown oil (44%). <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ7.92-7.22 (m, 7H), 6.99 (d, 2H, J=8.9 Hz), 4.51 (s, 2H), 4.26 (s, 2H), 3.83 (s, 3H), 3.76 (s, 3H). MS (ESI) 385 (M+H)<sup>+</sup>.

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#### Example 312

##### Preparation of 3-methylacetate-3-(2,6-dimethyl)-anilino-5-benzylthio-1,2,4-triazole

Following the procedure of Example 302(a)-(b) except 3-(2,6-dimethyl)-anilino-5-benzylthio-1,2,4-triazole was used in step 302(a) instead of 3-anilino-5-benzylthio-1,2,4-triazole and methyl bromoacetate was used in step 302(b) instead of iodomethane, the title compound was isolated as a white solid (43%). <sup>1</sup>H-NMR (400MHz, d6-DMSO) δ7.32-7.19 (m, 8H), 4.37 (s, 2H), 4.25 (s, 2H), 3.77 (s, 3H), 2.27 (s, 6H). MS (ESI) 383 (M+H)<sup>+</sup>.

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#### Biological Data:

##### Direct Spectrophotometric Assays of hMetAP2:

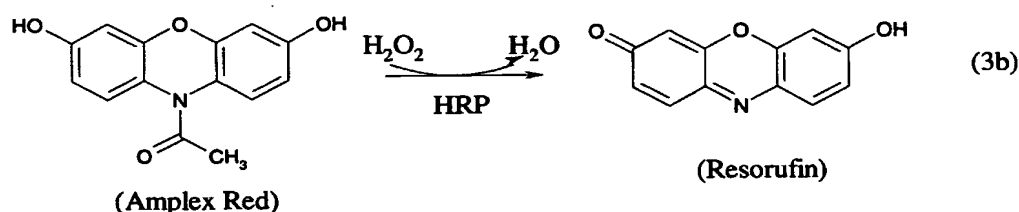
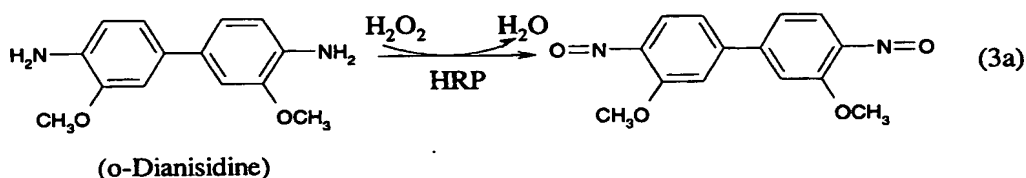
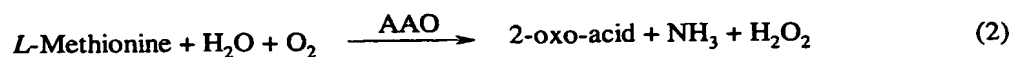
The hMetAP2 activity can be measured by direct spectrophotometric assay methods using alternative substrates, L-methionine-p-nitroanilide (Met-pNA) and L-methionine-7-amido-4-methylcoumarin (Met-AMC). The formation of p-nitroaniline (pNA) or 7-amido-4-methylcoumarin (AMC) was continuously monitored by increasing absorbance or fluorescence at 405 nm and 460 nm, respectively, on a corresponding plate reader. All assays were carried out at 30°C. The fluorescence or spectrophotometric plate reader was calibrated using authentic pNA and AMC from Sigma, respectively. For a typical 96-well plate assay, the increase in the absorbance (at 405 nm for pNA) or the fluorescence

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emission ( $\lambda_{\text{ex}} = 360 \text{ nm}$ ,  $\lambda_{\text{em}} = 460 \text{ nm}$ , for AMC) of a 50  $\mu\text{L}$  assay solution in each well was used to calculate the initial velocity of hMetAP2. Each 50  $\mu\text{L}$  assay solution, contained 50 mM Hepes- $\text{Na}^+$  (pH 7.5), 100 mM NaCl, 10-100nM purified hMetAP2 enzyme, and varying amounts of Met-AMC (in 3% DMSO aqueous solution) or Met-pNA. Assays were initiated with the addition of substrate and the initial rates were corrected for the background rate determined in the absence of hMetAP2.

**Coupled Spectrophotometric Assays of hMetAP2:**

The methionine aminopeptidase activity of hMetAP2 can also be measured spectrophotometrically by monitoring the free L-amino acid formation. The release of N-terminal methionine from a tripeptide (Met-Ala-Ser, Sigma) or a tetrapeptide (Met-Gly-Met-Met, Sigma) substrate was assayed using the L-amino acid oxidase (AAO) / horse radish peroxidase (HRP) couple (eq. 1-3a,b). The formation of hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) was continuously monitored at 450nm (absorbance increase of o-Dianisidine (Sigma) upon oxidation,  $\Delta\epsilon = 15,300 \text{ M}^{-1}\text{cm}^{-1}$ )<sup>2</sup> and 30 °C in a 96- or 384-well plate reader by a method adapted from Tsunasawa, S. et al.(1997) (eq. 3a). Alternatively, formation of  $\text{H}_2\text{O}_2$  was followed by monitoring the fluorescence emission increase at 587nm ( $\Delta\epsilon = 54,000 \text{ M}^{-1}\text{cm}^{-1}$ ,  $\lambda_{\text{ex}} = 563 \text{ nm}$ , slit width for both excitation and emission was 1.25 mm) and 30 °C using Amplex Red (Molecular Probes, Inc) (Zhou, M. et al. (1997) *Anal. Biochem.* 253, 162) (eq. 3b). In a total volume of 50  $\mu\text{L}$ , a typical assay contained 50 mM Hepes- $\text{Na}^+$ , pH 7.5, 100 mM NaCl, 10  $\mu\text{M}$   $\text{CoCl}_2$ , 1 mM o-Dianisidine or 50  $\mu\text{M}$  Amplex Red, 0.5 units of HRP (Sigma), 0.035 unit of AAO (Sigma), 1 nM hMetAP2, and varying amounts of peptide substrates. Assays were initiated by the addition of hMetAP2 enzyme, and the rates were corrected for the background rate determined in the absence of hMetAP2.



#### **Kinetic Data Analysis:**

Data were fitted to the appropriate rate equations using Grafit computer software. Initial velocity data conforming to Michaelis-Menton kinetics were fitted to eq. 4. Inhibition patterns conforming to apparent competitive and non-competitive inhibition were fitted to eq. 5 and eq. 6, respectively.

$$v = VA/(K_a + A) \quad (4)$$

$$v = VA/[K_a(1 + I/K_{is}) + A] \quad (5)$$

$$v = VA/[K_a(1 + I/K_{is}) + A(1 + I/K_{ii})] \quad (6)$$

In eqs. 4 - 6,  $v$  is the initial velocity,  $V$  is the maximum velocity,  $K_a$  is the apparent Michaelis constant,  $I$  is the inhibitor concentration, and  $A$  is the concentration of variable substrates. The nomenclature used in the rate equations for inhibition constants is that of Cleland (1963), in which  $K_{is}$  and  $K_{ii}$  represent the apparent slope and intercept inhibition constants, respectively.

#### **Cell growth inhibition assays:**

The ability of MetAP2 inhibitors to inhibit cell growth was assessed by the standard XTT microtitre assay. XTT, a dye sensitive to the pH change of mitochondria in eukaryotic cells, is used to quantify the viability of cells in the presence of chemical compounds. Cells seeded at a given number undergo approximately two divisions on average in the 72 hours of incubation. In the absence of any compound, this population of cells is in exponential growth at the end of the incubation period; the mitochondrial activity of these cells is reflected in the spectrophotometric readout ( $A_{450}$ ). Viability of a similar cell

population in the presence of a given concentration of compound is assessed by comparing the A450 reading from the test well with that of the control well. Flat-bottomed 96-well plates are seeded with appropriate numbers of cells ( $4-6 \times 10^3$  cells/well in a volume of 200  $\mu$ l) from trypsinized exponentially growing cultures. In the case of HUVECs, the wells are coated with matrigel prior to establishing the cultures. To "blank" wells is added growth medium only. Cells are incubated overnight to permit attachment. Next day, medium from wells that contain cells is replaced with 180  $\mu$ l of fresh medium. Appropriate dilutions of test compounds are added to the wells, final DMSO concentration in all wells being 0.2 %. Cells plus compound are incubated for an additional 72 hr at 37°C under the normal growth conditions of the cell line used. Cells are then assayed for viability using standard XTT/PMS (prepared immediately before use: 8 mg XTT (Sigma X-4251) per plate is dissolved in 100  $\mu$ l DMSO. 3.9 ml H<sub>2</sub>O is added to dissolve XTT and 20  $\mu$ l of PMS stock solution (30 mg/ml) is added from frozen aliquoted stock solution (10 mg of PMS (phenazine methosulfate, Sigma P-9625) in 3.3 ml PBS without cations. These stocks are frozen at -20°C until use). 50  $\mu$ l of XTT/PMS solution is added to each well and plates incubated for 90 minutes (time required may vary according to cell line, etc.) at 37°C until A<sub>450</sub> is >1.0. Absorbance at 450 nm is determined using a 96-well UV plate reader. Percent viability of cells in each well is calculated from these data (having been corrected for background absorbance). IC<sub>50</sub> is that concentration of compound that reduces cell viability to 50% control (untreated) viability.

The compounds of this invention show MetAP2 inhibitor activity having IC<sub>50</sub> values in the range of 0.0001 to 100  $\mu$ M. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of this invention are inhibitors of MetAP2 and which bind thereto with an IC<sub>50</sub> value in the range of 0.0001 to 100  $\mu$ M.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments

- specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, given the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the
- 5 present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

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